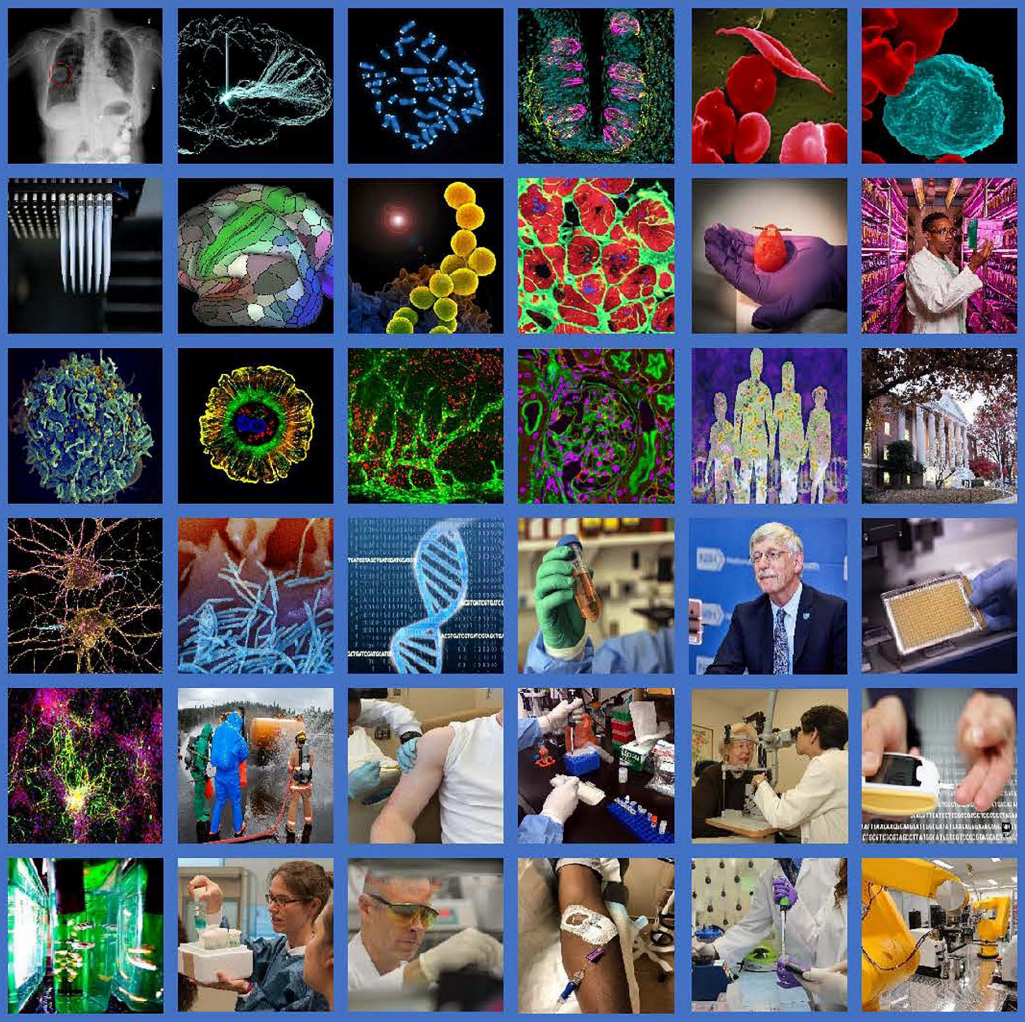
Report of the Director
National Institutes of Health

Fiscal Years 2016 – 2018



National Institutes of Health
Turning Discovery Into Health

Report of the Director

National Institutes of Health

Fiscal Years 2016, 2017, and 2018

Preface

This is the first National Institutes of Health (NIH) Triennial Report, as required by Section 403 of the *Public Health Service (PHS) Act*.[1] NIH's goal is for this report to serve as a useful reference for understanding NIH activities and operations. NIH welcomes feedback on the report.

Chapter Organization

Chapter 1 opens with a statement from the NIH Director assessing the state of biomedical and behavioral research. This chapter focuses on NIH structure, policies, and procedures, including operations of NIH extramural and intramural research programs. This chapter also addresses NIH activities to foster commitment to science, including both science education and literacy efforts, and training research workforce recruitment, training, and retention efforts.

Chapter 2 provides an overview of the NIH research portfolio that covers the following topics:

- Basic research
- Preclinical translational research
- Clinical research
- Postclinical translational research
- Clinical and community practice
- Identifying public health needs (epidemiology)
- Infrastructure, research resources, and technology development

[1] Section 203 of the *21st Century Cures Act* (P.L. 114-255) amended section 403 of the *Public Health Service (PHS) Act* to change the reporting requirement from every 2 years to every 3 years. Prior to this, five NIH Biennial Reports were produced. See Appendix A of this report for language in the *PHS Act* that is relevant to this report. Previous Biennial Reports can be found at: https://report.nih.gov/biennialreport/.

Chapter 2 begins with a brief introduction to the continuum of biomedical research at NIH. The research continuum moves from basic research, to preclinical translational research, to clinical research, and finally to postclinical translational research. As reflected by the last step of the continuum, NIH[2] works to ensure the uptake of research results by clinical practitioners and the public in order to bring the rich evidence base of NIH research to clinical and community practice, ultimately turning discovery into health. The introduction is followed by a more in-depth discussion of these stages of the bench-to-practice continuum at NIH, including information on the types of activities conducted at each stage across NIH Institutes and Centers (ICs) and the Office of the Director (OD).

Chapter 2 discusses key factors that drive the NIH research continuum. The chapter points out the importance of epidemiological research, which provides evidence of the association between disease and human biology, behavior, or environmental circumstances. The chapter concludes with an overview of the importance of NIH investment in research resources, infrastructure, and the development of new technologies, without which progress along the research continuum would not be possible.

Chapter 3 presents a cross-section of NIH research activities during the fiscal years (FY) 2016, 2017, and 2018 reporting period that covers the following topics:

- Cancer
- Neuroscience
- Life Stages, Human Development, and Rehabilitation
- Chronic Diseases and Organ Systems
- Autoimmune Diseases
- Infectious Diseases and Biodefense
- Public Health Emergency Preparedness
- Rare and Undiagnosed Diseases
- Microbiome
- Minority Health and Health Disparities
- Emerging Technologies
- Research Resources and Infrastructure

Each of these topics, many of which are categories specified in the *PHS Act*, is addressed in a separate section. They are grouped together in one chapter to address the intent of the statute in terms of presenting information on diseases, disorders, and adverse health conditions in a standardized format.

Chapter 4 addresses certain NIH Centers of Excellence, which are diverse in focus, scope, and origin. This report describes those NIH Centers of Excellence that were established by statutory mandate, representing a subset of NIH's full complement of such centers. This chapter also provides overviews, progress reports for FY 2016, 2017, and 2018 (covering programmatic and research activities and

[2] In partnership with the other agencies of the U.S. Department of Health and Human Services (HHS).

outcomes), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in the order of their establishment:

- Alzheimer's Disease Centers (1984)
- Claude D. Pepper Older Americans Independence Centers of Excellence (1989)
- Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (2001)
- National Institute on Minority Health and Health Disparities Centers of Excellence (2001)
- Rare Diseases Clinical Research Network (2003)
- Autism Centers of Excellence (2006)

The **Appendices** present reference documents and supporting data.

- Appendix A provides excerpts from the *PHS Act* that set the legal mandate for this Biennial Report and the inclusion of certain contents within it.
- Appendix B provides the Report of the Advisory Committee on Research on Women's Health.
- Appendix C provides information on actions undertaken to conduct or support research related to tickborne diseases and other vector-borne diseases.
- Appendix D provides the Report of Trans-NIH Research.
- Appendix E provides data on the National Research Service Award program (the primary NIH research training program), the National Library of Medicine training programs, and NIH graduate medical education activities.
- Appendix F provides the NIH report, Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research.
- Appendix G provides a catalog of disease registries and other data systems.
- Appendix H provides information on actions undertaken to carry out scientific frameworks on recalcitrant cancer.
- Appendix I provides NIH funding levels for chronic diseases and organ systems.
- Appendix J provides information on EurekaPrize Competitions.
- Appendix K provides a list of acronyms that are used in this report.

Contents

Chapter 1 About NIH

Statement of the Director

It is my honor to present to Congress the Triennial Report of the Director of the National Institutes of Health (NIH) for Fiscal Years (FY) 2016, 2017, and 2018. With congressional support, NIH continues to pursue its mission of discovering fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce illness and disability.

For more than 130 years, NIH has been at the forefront of biomedical research, directing critical funding to research institutions throughout the nation and the world, and stimulating lifesaving research breakthroughs. Starting life as a one-room Laboratory of Hygiene in 1887, NIH has grown into a complex and multidisciplinary engine for biomedical discovery and innovation comprising 27 Institutes and Centers (ICs) that span the broad spectrum of basic, translational, clinical, behavioral, and social sciences research, dealing with many aspects of biology and almost every human disease and disability. As the largest public funder of biomedical research in the world, NIH has been the driving force behind decades of advances that have improved the health of people throughout the United States (U.S.) and around the globe.

Remarkable Contributions

NIH research advances have prompted a revolution in the diagnosis, treatment, and prevention of disease. Thanks to discoveries funded through NIH appropriations, NIH-supported research has met some of our nation's biggest health challenges. A baby born in 2017 can look forward to an average life span of more than 78 years, almost three decades longer than a baby born in 1900.[1] The infant mortality rate in the U.S. has decreased from 26 of every 1,000 births in 1960[2] to 5.8 per 1,000 births in 2017,[3] and the outlook for premature infants also has improved substantially. This is thanks in part to NIH research on reducing preterm births, neonatal mortality, and other complications.

In recent years, impressive gains have been made in the fight against many common diseases. For example, in the mid-20th century, cardiovascular disease caused nearly 40 percent of U.S. deaths, claiming the lives of many people still in their 50s and 60s.[4] Between 1968 and 2013, deaths due to both coronary

[1] National Center for Health Statistics. Health, United States, 2018. Hyattsville, MD. 2019. Available at: https://www.cdc.gov/nchs/data/hus/hus18.pdf.
[2] MacDorman ME, et al. *Vital Health Stat* 1993;20(20).
[3] Kochanek KD, et al. Deaths: Final Data for 2017. *National Vital Statistics Reports*. 2019;68(9) https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_09-508.pdf.
[4] Fox CS, et al. *Circulation* 2004;110(5)522–7. PMID: 15262842.

heart disease and stroke decreased by approximately 78 percent.[5] NIH-supported research led to minimally invasive techniques to prevent heart attacks as well as highly effective drugs to lower cholesterol, control high blood pressure, and break up artery-clogging blood clots. NIH-funded interventions also have motivated people to make lifestyle changes that promote health, such as eating less fat, exercising more, and quitting smoking. For example, NIH's Diabetes Prevention Program has shown that lifestyle changes, such as diet and physical activity, can lower the risk of developing type 2 diabetes by 58 percent in adults at high risk for the disease.[6]

In part due to NIH-supported contributions, the death rate for all cancers combined has been declining since the early 1990s for adults and since the 1970s for children. By one estimate, 2.9 million cancer deaths were averted from 1991 to 2017 by improvements in cancer treatment, detection, and prevention.[7] NIH-funded research has helped to identify major cancer subtypes, which has led to development of new, often tailored treatments for a variety of cancers, including breast cancer, lung cancer, prostate cancer, and chronic myelogenous leukemia. NIH is also leveraging researchers' understanding of how to restore or enhance the immune system's ability to fight cancerous cells.[8]

One of NIH's greatest achievements over the past 30 years has been to lead the global research effort against the HIV/AIDS pandemic. Starting with basic research about how HIV works, discoveries along the biomedical and behavioral research continuum have led to the development of effective prevention strategies, rapid HIV tests, a new class of HIV-fighting drugs, and ultimately, life-saving drug combinations.[9] An HIV diagnosis was once a death sentence; now, a 20-year-old with HIV living in the U.S., receiving these treatments, is expected to live into their early 70s—nearly as long as someone without HIV.[10] Moreover, an overwhelming body of evidence has emerged to show that individuals with HIV who receive antiretroviral therapy (ART) and have achieved and maintained an undetectable viral load cannot sexually transmit the virus to others.[11] In addition to encouraging progress on an HIV vaccine, NIH has led groundbreaking research on using HIV therapies to prevent infections in uninfected individuals at high risk of infection, including the newborn children of mothers with HIV. According to the Centers for Disease Control and Prevention (CDC), since the mid-1990s, NIH research has informed the implementation of HIV testing and preventive interventions that resulted in a more than 90 percent decrease in the number of newborn children perinatally infected with HIV in the U.S.[12]

NIH has made great strides in preventing and treating a variety of infections that affect the lives of Americans. NIH-funded research played a key role in developing the vaccine against haemophilus influenza B, once the leading cause of childhood bacterial meningitis, reducing cases by more than

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[5] https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf.
[6] https://www.niddk.nih.gov/about-niddk/research-areas/diabetes/diabetes-prevention-program-dpp/Pages/default.aspx.
[7] Siegel RL, et al. *CA Cancer J Clin* 2020;70(1):7-30. PMID: 31912902. https://acsjournals.onlinelibrary.wiley.com/doi/pdf/10.3322/caac.21590.
[8] http://www.cancer.gov/research/areas/treatment/immunotherapy-using-immune-system.
[9] Schwetz et al. *J Infect Dis* 2019;219(1):6-9. PMID: 30165415.
[10] Samji H, et al. *PLoS One* 2013;8(12). PMID: 24367482.
[11] Eisinger RW, et al. *JAMA* 2019;321(5):451-452. PMID: 30629090.
[12] https://www.niaid.nih.gov/diseases-conditions/prevention-perinatal-transmission.

99 percent.[13] NIH-supported researchers were the first to identify and characterize rotavirus, the most common cause of severe childhood diarrhea worldwide, and partnered with industry to create the first rotavirus vaccine in 1998. NIH-funded research played a crucial role in developing vaccines for hepatitis A and B and effective therapies for hepatitis C, which have greatly reduced the number of hepatitis A and B infections and can fully cure hepatitis C.

NIH has a long history of being a trailblazer for biomedical innovation. Major achievements include the first human liver transplantation, performed by an NIH grantee in 1967; the first large clinical trials of lithium as a mood stabilizer; and the development of cochlear implants for hearing loss in children and adults.[14] NIH-funded research established the first U.S. Food and Drug Administration (FDA)-approved treatment for the most common type of stroke, a drug called tissue plasminogen activator, in 1995,[15] and the first successful molecular medicine Gleevec (approved by FDA in 2001).[16] NIH scientists also pioneered therapies for rare diseases, including developing and testing the first therapy for Gaucher disease that delivered the missing enzyme directly into the white blood cells of patients,[17] and the first FDA-approved treatment for lipodystrophy using a synthetic form of the fat-derived hormone leptin.[18] NIH-funded research also helped pave the way to the development of tofacitinib (approved by FDA in 2012), the first new rheumatoid arthritis drug in more than a decade that can be taken as a pill (rather than as an injection) to slow or halt joint damage.

An Economic Powerhouse

In realizing its mission, NIH promotes a healthier population, resulting in a healthier workforce and thus a stronger economy. NIH also directly affects the economy, having propelled research advances by supporting a robust research community that generates biomedical knowledge, patentable inventions, and trained scientists, including more than 155 NIH-funded Nobel laureates as of 2018.[19] In FY 2018, NIH funding supported research personnel at more than 2,690 institutions, located across all 50 states and U.S. territories and more than 90 countries around the world. Furthermore, it has been estimated that in 2015, NIH supported 352,000 jobs across all 50 states, including almost every congressional district.[20]

Investing in NIH propels the U.S. economy through job creation and continued innovation in the biotechnology sector. For example, one report indicated that the U.S.'s $12.3 billion investment in the human genome project from 1988 to 2012 has resulted in nearly $1 trillion of economic growth—a 178-fold return on investment.[21] Every dollar invested by NIH gives back to our nation in multiple; for

[13] https://www.nih.gov/sites/default/files/about-nih/impact/childhood-hib-vaccines-case-study.pdf.
[14] https://www.nih.gov/sites/default/files/about-nih/impact/neurostimulation-technologies-case-study.pdf.
[15] http://www.cdc.gov/stroke/types_of_stroke.htm.
[16] https://www.nih.gov/sites/default/files/about-nih/impact/fighting-cancer-case-study.pdf.
[17] https://irp.nih.gov/accomplishments/therapy-for-inherited-enzyme-deficiencies.
[18] https://irp.nih.gov/accomplishments/from-hormone-to-pharmaceutical-lipodystrophy.
[19] https://www.nih.gov/about-nih/what-we-do/nih-almanac/nobel-laureates.
[20] http://www.unitedformedicalresearch.com/wp-content/uploads/2016/05/NIH-Role-in-the-Economy-FY15-FINAL-5.23.16.pdf.
[21] http://web.ornl.gov/sci/techresources/Human_Genome/publicat/2013BattelleReportImpact-of-Genomics-on-the-US-Economy.pdf.

example, NIH extramural funding is estimated to have generated some $74 billion in new economic activity nationwide in 2019—nearly double taxpayers' investment.[22] In rural states, each $1.00 of NIH spending generated an average $1.80 of total economic impact.[23]

NIH-supported research spurs further investments in private sector biomedical innovation. Several studies have found that NIH investments in a particular research area stimulate private-sector investment in that area.[24,25] One such study estimated that a $1.00 increase in public *basic* research stimulates an additional $8.38 of industry research and development (R&D) investment after 8 years, and a $1.00 increase in public *clinical* research stimulates an additional $2.35 of industry R&D investment after 3 years. NIH also partners with the private sector to drive discovery forward, such as through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, which have had a demonstrable impact in terms of overall economic output.[26]

NIH funding is the foundation for long-term U.S. global competitiveness in such industries as biotechnology, medical devices, and pharmaceutical development. Innovation in biomedical research in a knowledge-based world economy has the demonstrable capacity to generate growth, high-quality jobs, better health, and better quality of life for all Americans. Investments in biomedical research infrastructure, in scientists' ideas, and in workforce training spur innovation that will drive America's growth.

Rising to Public Health Challenges

NIH responds to public health needs, ranging from emerging diseases and conditions to the growing burden of chronic disease management. For example, in 2016, Zika infected millions of people and left many babies with birth defects. The World Health Organization (WHO) declared the viral infections a public health emergency of international concern. In response to this emerging public health challenge, NIH-supported scientists collaborated with public, academic, and industry partners to better understand the Zika virus and ways to combat it.

Opioid use disorder is another public health challenge. In 2018, an estimated 10.3 million people 12 years and older in the U.S. misused opioids, including heroin.[27] To reverse the opioid crisis that continues to grip the nation, in 2018, NIH launched the Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠.[28] The trans-NIH research effort aims to improve treatments for chronic pain, curb the rates of opioid use disorder and overdose and achieve long-term recovery from opioid addiction. The HEAL

[22] https://www.unitedformedicalresearch.org/wp-content/uploads/2019/04/NIHs-Role-in-Sustaining-the-US-Economy-2019-Update-FINAL.pdf.
[23] https://www.unitedformedicalresearch.org/wp-content/uploads/2019/03/NIH-Research-Rural-States-Executive-Summary-FINAL-3.13.19.pdf.
[24] http://www.nber.org/papers/w20889.
[25] Toole AA. *J Law Econ* 2007;50:81–104.
[26] https://sbir.cancer.gov/impact.
[27] https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf.
[28] https://heal.nih.gov/.

Initiative is taking an "all hands-on deck" approach to the opioid crisis, garnering expertise from across NIH to accelerate research and address this urgent public health emergency.

Fostering Good Stewardship

To achieve its mission and maintain its role as the world's premier biomedical research agency, NIH must support the best scientific ideas and brightest scientific minds while maintaining public trust. As a steward of public resources, NIH must ensure that it supports not only the best science, but science that is done ethically and responsibly.

NIH's ability to help ensure that the nation remains a global leader in scientific discovery and innovation is dependent upon a pool of highly talented scientists from diverse backgrounds who will help to further NIH's mission. In June 2017, NIH launched the Next Generation Researchers Initiative (NGRI)[29] aimed at strengthening the biomedical workforce with a focus on early-career investigators—investigators who are at an early stage in their career. NIH takes a multipronged approach to increase the number of NIH-funded early-stage investigators and to stabilize the career trajectory of scientists at all stages. By developing evidence-based, data-driven strategies incorporated into initiatives like NGRI, NIH seeks to maximize scientific output by assessing current NIH funding programs to identify, grow, and retain new- and early-career investigators across these critical career stages.[30]

As a global leader of biomedical research, NIH has a responsibility for maintaining and bolstering the public's confidence in research results. To uphold this responsibility, NIH takes the lead in promoting new approaches toward enhancing the rigor of experimental design, analysis, and reporting. These efforts are not aimed at rare instances of research misconduct or willful deception, which require separate oversight mechanisms, but are intended to improve the biomedical research community's overall culture and training to encourage best practices for rigorous scientific methods.

In addition, NIH develops policies to enhance rigor. Women now account for roughly half of all participants in NIH-supported clinical research, which is subject to NIH's *Policy on the Inclusion of Women in Clinical Research*.[31] However, more often than not, basic and preclinical biomedical research has focused on male animals and cells. An over-reliance on only male animals and cells originating from males in research may obscure understanding of how sex influences health processes and outcomes. Since January 2016, NIH has required researchers to account for the possible role of sex as a biological variable (SABV) in studies involving vertebrate animals and humans.[32] Accounting for sex as a biological variable requires the development of appropriate research questions, study designs, and analytical considerations, as well as full reporting of findings. By ensuring adequate consideration of both sexes in research and analysis, scientific rigor will be enhanced and the translation of preclinical research into clinical applications strengthened, ultimately optimizing the health of women, men, girls, and boys.

[29] https://grants.nih.gov/ngri.htm.
[30] Michael Lauer, et al. *PNAS* 2017;114:11801–11803.
[31] https://grants.nih.gov/policy/inclusion/women-and-minorities.htm.
[32] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html.

To improve efficiency, the *21st Century Cures Act* provided a new EUREKA prize authority[33] and allowed NIH to use Other Transactions Authority (OTA) in two areas that need extra flexibility and collaboration: the NIH Common Fund and the *All of Us* Research program.[34] Launched in 2015 as part of the Precision Medicine Initiative (PMI), the *All of Us* Research Program is a historic effort to gather data from 1 million or more people living in the U.S. to accelerate research and improve health.[35] This ambitious goal requires flexibility, complex and dynamic interactions, and ways to engage non-traditional NIH awardees to advance the mission. In this vein, *All of Us* has used OTA to make awards to the Healthcare Provider Organizations to help build the research protocols, test enrollment procedures, and collect essential health data and biological specimens. Innovative approaches by NIH, such as the use of OTA and prize competitions, allow a nimble, flexible, and alternative approach to solving complex problems, thereby contributing to the advancement of NIH's mission.

Although many challenges to improve health still lie ahead, investing in NIH research offers hope to patients, families, and caregivers that a solution is within reach. Within this report, you will find many examples of how NIH capitalizes on the many promising opportunities to improve human health while helping to meet the needs of the biomedical research community to get the job done.

—Francis S. Collins, M.D., Ph.D.

[33] See Appendix J for more details on EUREKA Prize Competitions.
[34] https://www.nih.gov/about-nih/who-we-are/nih-director/testimony-21st-century-cures-implementation-updates-fda-nih.
[35] https://allofus.nih.gov/.

NIH's Mission

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and to use that knowledge to enhance health, lengthen life, and reduce illness and disability.[36]

The goals of the agency are to—

- Foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health
- Develop, maintain, and renew scientific human and physical resources that will ensure the nation's capability to prevent disease
- Expand the knowledge base in medical and associated sciences in order to enhance the nation's economic well-being and ensure a continued high return on the public investment in research
- Exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science

In realizing these goals, NIH provides leadership and direction to programs designed to improve the health of the nation by conducting and supporting—

- Research on the causes, diagnosis, prevention, and cure of human diseases
- Research on the processes of human growth and development
- Research on the biological effects of environmental contaminants
- Research on the understanding of mental, addictive, and physical disorders
- Programs for the collection, dissemination, and exchange of information in medicine and health, including the development and support of medical libraries and the training of medical librarians and other health information specialists

[36] https://www.nih.gov/about-nih/what-we-do/mission-goals.

Overview of NIH Structure and Organization

NIH is the primary federal agency for leading, conducting, and supporting biomedical and behavioral research. Composed of the Office of the Director (OD) and 27 ICs, NIH employs approximately 18,000 people and is the steward of an approximately $37 billion budget (as of FY 2018).[37] The leadership and financial support NIH provides to biomedical, behavioral, and social science researchers extends throughout our nation and the world.

Figure 1. The James H. Shannon Building (Building One) on the NIH Campus in Bethesda, Maryland. Credit: Lydia Polimeni, NIH.

Institutes and Centers

The 27 NIH ICs are organized with a focus on and expertise in a specific disease (e.g., cancer, diabetes), an organ system (e.g., heart, eye), a life stage (e.g., pregnancy, childhood, aging adulthood), an overarching field of science (e.g., genomics, nursing, environmental health), or a technology (e.g., biomedical imaging, bioengineering, information technology). The priorities of each IC are guided by its mission[38] and strategic plan,[39] which are harmonized with NIH's overall mission[40] and the NIH-Wide Strategic Plan.[41] The ICs *support* research and research training through extramural activities; most ICs also *conduct* research and research training through intramural activities.

[37] http://www.nih.gov/about/almanac/appropriations/part2.htm.
[38] https://www.nih.gov/institutes-nih/list-nih-institutes-centers-offices.
[39] https://report.nih.gov/strategicplans/.
[40] https://www.nih.gov/about-nih/what-we-do/mission-goals.
[41] https://www.nih.gov/about-nih/nih-wide-strategic-plan.

Listing of ICs

The following is a list of NIH ICs, presented in the order in which they appear on the appropriation table in the Congressional Justification:

- National Cancer Institute (NCI)
- National Center for Complementary and Integrative Health (NCCIH)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of General Medical Sciences (NIGMS)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- National Eye Institute (NEI)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute on Aging (NIA)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- National Institute on Deafness and Other Communication Disorders (NIDCD)
- National Institute of Mental Health (NIMH)
- National Institute on Drug Abuse (NIDA)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute of Nursing Research (NINR)
- National Human Genome Research Institute (NHGRI)
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- National Institute on Minority Health and Health Disparities (NIMHD)
- National Center for Advancing Translational Sciences (NCATS)
- John E. Fogarty International Center (FIC)
- National Library of Medicine (NLM)
- NIH Clinical Center (CC)
- Center for Information Technology (CIT)
- Center for Scientific Review (CSR)

Office of the Director

OD is composed of several offices that provide expert advice to the NIH Director and his leadership team. It coordinates policy across the NIH research community and administers centralized support services essential to the NIH mission.

Listing of OD Offices

The following is a list (presented in the order in which they appear on the appropriation table in the Congressional Justification) of select OD offices that advise the NIH Director, develop NIH policy, and provide essential NIH-wide oversight and coordination:

- Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
- Office of Extramural Research (OER)
- Office of Intramural Research (OIR)
- Office of Management (OM)
- Office of Science Policy (OSP)
- Office of Communications and Public Liaison (OCPL)
- Office of Equity, Diversity, and Inclusion (EDI)
- Office of Legislative Policy and Analysis (OLPA)
- Office of Ombudsman/Center for Cooperative Resolution (CCR)
- NIH Ethics Office (NEO)
- Office of the Chief Information Officer (OCIO)

Division of Program Coordination, Planning, and Strategic Initiatives

The role of DPCPSI[42] is to identify emerging scientific opportunities, rising public health challenges, and scientific knowledge gaps that merit further research; assist NIH in effectively addressing identified areas; and develop and apply resources (databases, analytic tools, and methodologies) that will support priority setting and analyses of the NIH portfolio. The program offices within DPCPSI are the Office of Strategic Coordination, which manages the NIH Common Fund; the Office of AIDS Research (OAR); the Office of Behavioral and Social Sciences Research (OBSSR); the Office of Research Infrastructure Programs (ORIP); the Office of Disease Prevention (ODP); the Office of Dietary Supplements (ODS), the Office of Research on Women's Health (ORWH), the Sexual and Gender Minority Research Office (SGMRO), and the Tribal Health Research Office (THRO). Many of these OD program offices fund research using IC award-making authorities. ICs often partner with one of these program offices to supplement their funding for a specific program or project. However, ORIP directly funds research through a separate award authority from those used by ICs. NIH Common Fund programs are largely supported only using Common Fund appropriations, with ICs partnering to provide programmatic management.

[42] https://dpcpsi.nih.gov/.

The NIH Common Fund was enacted into law by Congress through the 2006 *NIH Reform Act* to support crosscutting, trans-NIH programs that require participation by at least two NIH ICs or would otherwise benefit from strategic planning and coordination. The requirements for the Common Fund encourage collaboration across the ICs while providing the NIH with flexibility to determine priorities for Common Fund support. To date, the Common Fund has been used to support a series of short-term, exceptionally high-impact, trans-NIH programs, including the High-Risk, High-Reward Research program, which includes several awards to test new ways of fostering innovation and also was authorized through the *Reform Act*.

NIH Common Fund programs are intended to be—

- *Transformative.* Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade.
- *Catalytic.* Must achieve a defined set of high-impact goals within a defined period of time (5 to 10 years).
- *Synergistic.* Outcomes must synergistically promote and advance individual missions of NIH ICs to benefit health.
- *Crosscutting.* Program areas must cut across missions of multiple NIH ICs, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach.
- *Unique.* Must be something no other entity is likely or able to do.

OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. OAR sets scientific priorities, enhances collaboration, and ensures that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools in the global fight against AIDS.

ORIP is dedicated to supporting research infrastructure and research-related resources programs, and to coordinating NIH's science education efforts. Together, ORIP's programs support researchers with resources they need to improve human health.

The mission of ODP is to improve public health by increasing the scope, quality, dissemination, and impact of prevention research supported by NIH. ODP also provides scientific leadership and oversight for the continued implementation of the NIH–FDA Tobacco Regulatory Science Program, which addresses priority areas of the Family Smoking Prevention and Tobacco Control Act, including the manufacture, distribution, and marketing of tobacco products.

The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

The mission of OBSSR is to enhance the impact of health-related behavioral and social sciences research; coordinate behavioral and social sciences research conducted or supported by the NIH and integrate these sciences within the larger NIH research enterprise; and communicate health-related behavioral and social sciences research findings to various stakeholders within and outside the federal government.

Established in 1990, ORWH is the first PHS office dedicated specifically to promoting women's health research within and beyond the NIH scientific community. ORWH publishes the *Report of the Advisory Committee on Research on Women's Health*; as required by Section 486(d)(5)(B) and 486B(b) of the *PHS Act*, this report is included in Appendix B.

DPCPSI's newest program offices—THRO[43] and SGMRO[44]—were established in 2015 to coordinate NIH activities relating to tribal health and sexual and gender minorities, respectively. A more detailed description of these offices is included in the Minority Health and Health Disparities section of Chapter 3. DPCPSI also plans, supports, and provides technical assistance in the development of program evaluations and manages planning and reporting activities that support the U.S. Department of Health and Human Services' (HHS) implementation of the *Government Performance and Results Act (GPRA)* and the *GPRA Modernization Act*, as well as other government-wide performance assessment activities (see Training and Career Development Programs Section in this chapter) and portfolio analysis activities.

Office of Extramural Research

OER[45] is the OD office that provides the corporate framework for NIH administration of research grants and contracts, ensuring scientific integrity, public accountability, and effective stewardship of the NIH extramural research portfolio. Offices within OER include the Office of Policy for Extramural Research Administration; the Office of Research Information Services; the Office of Laboratory Animal Welfare; the Strategic Management and Contracts Office; the Office of Electronic Research Administration; the Division of Communications and Outreach; the Office of Small Business Education and Entrepreneurial Development; the Division of Biomedical Research Workforce; the Division of Human Subjects Research; and the Office of the NIH Guide.[46]

Office of Intramural Research

OIR[47] is the OD office responsible for oversight and coordination of intramural research conducted within NIH laboratories and clinics. Offices within OIR include the Office of Intramural Training and Education; the Office of Technology Transfer; the Office of Human Subjects Research Protections; the Office of Animal Care and Use; and the Office of NIH History and Stetten Museum.

Historical information about NIH—including the establishment of the categorical Institutes, Centers, and specialized offices—is maintained by the NIH Office of History, a component of OIR that preserves records of significant NIH achievements, innovative exhibits, and educational programs to enhance understanding of NIH biomedical and behavioral research.[48]

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[43] https://dpcpsi.nih.gov/thro.
[44] https://dpcpsi.nih.gov/sgmro.
[45] https://grants.nih.gov/grants/oer.htm.
[46] https://grants.nih.gov/aboutoer/welcome.htm.
[47] https://oir.nih.gov/about.
[48] https://history.nih.gov/research/sources_legislative_chronology.html.

Collaboration Between Institutes, Centers and Offices

Although NIH comprises myriad Institutes, Centers, and Offices (ICOs), all working toward achieving their mission, they do not operate in silos but rather interact in a highly collaborative fashion. Today, more than ever, NIH ICOs are working together in new ways and leveraging their unique strengths and resources. These collaborations can be formal or informal and may involve sharing financial resources, materials, or specimens. Often, collaboration takes the form of sharing actual scientific expertise. By maximizing resources, these trans-NIH initiatives serve to advance medical research in all disease areas and across the basic, translational, and clinical research continuum.

Trans-NIH Research Reporting

To comply with Section 402A(c)(2)(B) of the *PHS Act,* as amended by the *21st Century Cures Act* (P.L. 114-255), Appendix D includes a report on the amount made available by the NIH ICs for conducting or supporting research that involves collaboration between two or more ICs.

Extramural and Intramural Research Programs

As noted, NIH supports research and research training through extramural activities and conducts research and research training through intramural activities. This section provides overviews of the extramural and intramural programs.

Extramural Research Program

More than 80 percent of NIH funding is awarded by the ICs to the extramural biomedical and behavioral research community. The extramural research community is composed of scientists, clinicians, and other research personnel affiliated with more than 2,690 organizations,[49] including universities, medical schools, hospitals, small businesses, and other research facilities located in all 50 states, the District of Columbia, Puerto Rico, Guam, the U.S. Virgin Islands, and other countries. In FY 2018, NIH funded the research of more than 30,000 principal investigators through research grants, which supported many thousands of additional personnel. With NIH support, these investigators and their research teams conduct the vast majority of research that leads to improvements in the prevention, detection, diagnosis, and treatment of disease and disability.

The NIH Deputy Director for Extramural Research provides leadership and coordinates policy, guidance, and oversight for IC grant and programmatic management operations and is a conduit for extramural policy issues with the biomedical research community beyond NIH. OER is where grants policy, program

[49] Based on FY 2018 numbers.

coordination, compliance, and services converge to support and sustain the NIH extramural research program.

Developed, managed and supported by OER, the electronic Research Administration (eRA) system provides information technology solutions and support for the full life cycle of grants administration functions for the NIH, as well as several other federal agencies. It is the largest research grants management system in the federal government in terms of the number of applications, accounting for more than 50 percent of the grant applications received by *Grants.gov*, the federal-wide portal for advertising funding opportunities. eRA supports grant administration for grantees and federal staff, from the submission of applications to the closeout of awards. eRA also provides services to other operating divisions of HHS and other federal agencies.

Grants Overview

The *NIH Guide for Grants and Contracts*[50] is the official publication for NIH funding opportunities. NIH advertises availability of grant and cooperative agreement support through funding opportunity announcements (FOAs), and also announces Requests for Proposals for R&D contract solicitations.[51] In addition to the *NIH Guide for Grants and Contracts*, applicants can also find FOAs on *Grants.gov*.

Most NIH grants funding is for projects that are investigator-initiated and submitted through omnibus parent announcements that span the breadth of the NIH mission. NIH uses program announcements (PAs), requests for applications (RFAs), and notices of special interest (NOSIs) to highlight areas of scientific interest. The main types of funding that NIH provides are Research Grants (R series), Career Development Awards (K series), Research Training and Fellowships (T and F series), Program Project/Center Grants (P series), and Cooperative Agreements (U series).

NIH uses activity codes (e.g., R01, R43) to differentiate the wide variety of research-related programs the agency supports. The most commonly used activity code is the R01, which designates a grant for a discrete, specified research project that is generally awarded for 3 to 5 years. Receiving a first R01 is a significant professional achievement for a scientist, traditionally marking attainment of scientific independence. Examples of other activity codes include the following:

- R41/R42 and R43/R44 awards for the Small Business Technology Transfer program and the Small Business Innovation Research program, respectively
- R21 awards for exploratory/developmental research projects
- R15 Academic Research Enhancement Awards to support small-scale research projects at educational institutions that have not been major recipients of NIH research grant funds
- F32 postdoctoral individual fellowship awards under the National Research Service Award (NRSA)

[50] http://grants.nih.gov/grants/guide.

[51] An FOA is a publicly available document by which a federal agency makes known its intentions to award grants or cooperative agreements. FOAs may be known as PAs, RFAs, notices of funding availability, solicitations, or parent announcements.

- T32 awards for enabling institutions to recruit individuals selected by the program leadership for predoctoral and/or postdoctoral research training in specified scientific areas
- K01 career development awards to provide support and protected time to individuals with a Ph.D. or D.V.M. for intensive, supervised research career development experiences
- K01 career development awards to provide support and protected time to individuals with a Ph.D. or D.V.M. for intensive, supervised research career development experiences
- K08 and K23 career development awards to provide support and protected time to individuals with a clinical doctoral degree for intensive, supervised research career development experiences
- P01 awards for research program projects that are broadly based, multidisciplinary, often long-term research, and have a specific major objective or a basic theme
- P30 awards for shared resources and facilities at research centers
- U01 awards for discrete, specified, circumscribed projects to be performed by investigator(s) in an area representing their specific interests and competencies

Contracts Overview

The Research and Development Contracts mechanism is another means by which NIH supports research and research-related activities. NIH typically uses research contracts to acquire goods or services for the direct benefit or use of the government. For example, contracts may be used to support research in areas of significant scientific interest, to further scientific knowledge, or to achieve a specific research goal. A research contract differs from a grant in a number of respects that are designed to comply with provisions of the Federal Acquisition Regulation. These differences include the manner used to solicit and negotiate the requirement, the level of NIH participation during contract performance, and the control of study results. Contracts are managed by the Office of Acquisitions Logistics and Management (OALM) in the OD.

NIH Peer-Review Process

All NIH grant, fellowship, and cooperative agreement applications and contract proposals for research and development funding undergo evaluation through peer review, in which external expert panels determine the scientific and technical merit of the applications and proposals in the first level of peer review and make recommendations concerning programmatic relevance and funding in the second level of peer review. The NIH peer review process strives to be fair, equitable, timely, and free of bias. The two-tiered system is mandated by both statute (Section 492 of the *PHS Act*) and by federal regulations.[52]

The Center for Scientific Review (CSR) is the portal for receipt and referral of NIH grant, fellowship, and cooperative agreement applications and is the locus for the first level of review for most applications. Applications relevant to the NIH mission receive two referral assignments. One assignment is to an IC whose mission encompasses the aims and objectives of the application and therefore may be interested in funding the application. The other assignment is to the Scientific Review Group (SRG) that will conduct the first level of review, including evaluation for scientific and technical merit. If the application is in

[52] https://grants.nih.gov/grants/peer-review.htm.

response to an RFA, the SRG most often will be convened by the IC(s) responsible for the RFA. NIH uses established referral criteria to determine the appropriate SRG to carry out review and the IC(s) most suitable to potentially fund the project.

SRGs are composed primarily of nonfederal scientists who have expertise in relevant scientific disciplines and current research areas. SRGs evaluate and make recommendations on the overall scientific and technical merit of the research proposed in the application, including the protection of human subjects, vertebrate animal welfare, biohazards, and the appropriateness of budget requests and period of support requested.

The Advisory Council/Board of the potential awarding IC performs the second level of review. Advisory Councils are composed of scientists from the extramural research community and public representatives. Program staff provide a grant-funding plan to the Advisory Council. Council members have access to applications and summary statements pending funding for that IC in that Council round. Identifying applications that further specific program priorities and potential public health impact is a particularly important function of this second level of peer review. Advisory Councils recommend projects for funding but do not make funding decisions.

Concepts are considered an early planning stage for some IC initiatives and describe their basic purpose, scope, and objectives. Councils play an important role in Concept Clearance processes, whereby ICs receive input from their Councils regarding the merits of potential research solicitations. However, Council approval of a concept does not guarantee it will become a funded initiative.

Funding Decisions

Applications that are scientifically meritorious, based on SRG review, and recommended by an IC's National Advisory Council are considered for funding. The outcome of the review process is important, but it is not the sole factor in determining an IC's funding decision. Other considerations include portfolio balance, public health needs, programmatic relevance, IC priorities, requirements specified in congressional appropriations, and availability of funds.

Some of the ICs publish paylines as part of their funding strategies to guide applicants on their likelihood of receiving funding. Application scores can be compared only against the payline for the FY when the application will be considered for funding, which is not necessarily the year when it was submitted. Advisory Councils consider, evaluate, and make recommendations on applications that score both within and outside the payline.[53]

[53] An application may be designated "Not Recommended for Further Consideration" (NRFC) at the first level of peer review if it lacks significant and substantial merit; presents serious ethical problems in the protection of human subjects from research risks; or presents serious ethical problems in the use of vertebrate animals, biohazards, and/or select agents. Applications designated as NRFC do not proceed to the second level of peer review (National Advisory Council/Board) because they cannot be funded.

Many ICs establish procedures for funding applications that score beyond the payline or outside of the funding limit. Terms used for this category of awards vary by IC but include *select pay*, *exception pools*, *high program priority*, and *special emphasis*. What is consistent is the use of these funds, with strong justification, to support highly innovative or high-program-priority applications that score beyond the payline or outside the funding limit.

Before issuing an award, NIH ensures that the planned research meets all requirements for safe and responsible conduct. This includes making sure that the research has undergone all necessary reviews and has obtained required approvals from boards and committees charged with protection of human subjects; inclusion of minorities, women, and children; humane animal care and use; biosafety; and other matters as appropriate. NIH also ensures that the institution where the research takes place has systems, policies, and procedures in place to manage federal funds and activities. Institutions also must have policies in place that manage research misconduct and promote objectivity in research by establishing standards to protect the design, conduct, and reporting of NIH-funded research from bias resulting from investigators' conflicting financial interests.

Post-Award Administration

NIH policies extend into the post-award phase of research as well, so that NIH can monitor research progress and provide oversight. Scientific and administrative monitoring includes reviewing yearly progress and periodic financial reports submitted by grantees. NIH extramural staff monitor grants to identify potential problems and areas where technical assistance might be necessary. This active monitoring is accomplished through review of reports and correspondence from the grantee, audit reports, site visits, and other information available to NIH.[54] NIH also monitors compliance with federal laws and policies pertaining to protection of human subjects, the care and use of vertebrate animals used in research, data sharing, the NIH Public Access Policy, and other matters. In addition, oversight of clinical research may involve data and safety monitoring and monitoring of inclusion of clinical research participants by sex, gender, race, and ethnicity.

Challenges and Prize Competitions

Although NIH primarily utilizes grants, contracts, and cooperative agreements to conduct and support biomedical research, challenges and prize competitions can be an effective alternative mechanism to spur innovation when a particular and prespecified solution to a scientific or technical problem is needed. Challenges and prize competitions allow a broad swath of innovators to solve complex problems identified by NIH and receive awards for the best solutions. They enable NIH to establish ambitious goals within a relatively short time frame without bearing high levels of risk by paying only for results that meet NIH's specifications. Challenges also can be used to increase the number and diversity of individuals or

[54] https://grants.nih.gov/grants/policy/nihgps/HTML5/section_8/8.4_monitoring.htm?tocpath=8%20Administrative%20Requirements%7C8.4%20Monitoring%7C__0#8.4_Monitoring.

organizations contributing to the advancement of NIH's mission, and they can attract public attention to and stimulate private investment in urgent or unmet public health needs.

The EUREKA prize section of the *21st Century Cures Act* (P.L. 114-255) empowers NIH to use its challenge authority to improve health outcomes for diseases of significant burden in the U.S., where research investment is small relative to treatment and prevention costs and where there is potential for significant cost savings to the government. To comply with Section 2002(b)(2) of the *21st Century Cures Act*, Appendix J includes on the effect of innovations developed from EUREKA prize competitions.

Intramural Research Program

The Intramural Research Program (IRP) is the internal research program of NIH, known for its synergistic approach to biomedical science. Approximately 10 percent of NIH funds support research and training activities carried out by IRP scientists.

The IRP seeks to be a dynamic research environment for new generations of imaginative scientists to conduct fundamental research that reveals new principles of biology, provides new understandings of human disease, and changes treatment and prevention paradigms. The IRP research environment is also designed to attract and train a highly talented and diverse cadre of scientists who will lead biomedical research in the 21st century. Its unique funding environment means the IRP can facilitate opportunities to conduct both long-term and high-impact science that would otherwise be difficult to undertake. The IRP has nurtured many Nobel Prize winners—winners of 25 prizes and counting—who either did the bulk of their award-winning research in the IRP or trained or worked in one of the IRP laboratories.[55]

The IRP laboratories (including the NIH Clinical Center) are located on NIH campuses in the Bethesda, Rockville, Frederick, and Baltimore areas in Maryland; Research Triangle Park, North Carolina; Detroit, Michigan; Phoenix, Arizona; Framingham, Massachusetts; and the Rocky Mountain Laboratories in Hamilton, Montana. Approximately 1,150 principal investigators lead intramural research projects that involve almost 6,000 trainees, ranging from high school students to postdoctoral and clinical fellows.

The NIH IRP conducts basic, translational, and clinical research. Organizationally, individual laboratories and clinics report to their respective IC and are responsible for conducting original research consistent with the goals of the IC. Most ICs have an intramural program. As with the extramural program, intramural research proposals are generated by scientists. In the IRP, however, program directions and research priorities are not shaped primarily through grant awards[56] but rather through professional hiring and promotion decisions, external reviews, and the allocation of resources to laboratories and branches.

The IRP in each IC has a promotion and tenure committee that evaluates all recommendations for professional appointment or promotion. Tenured and tenure-track scientists undergo formal internal reviews annually; resource allocations and promotions are determined based on these reviews. In

[55] https://irp.nih.gov/about-us/honors/nobel-prize.

[56] The exception is that intramural investigators are eligible to compete for some Common Fund initiatives to allow qualified intramural researchers to contribute to the goals of Common Fund programs.

addition, at least every 4 years, an external expert Board of Scientific Counselors reviews the work of each tenured or tenure-track scientist and makes recommendations regarding continuation or modification of projects and adjustment of resources (e.g., budget, space, and personnel). Moreover, IC Scientific Directors are evaluated by an external committee every 5 years, and each IC intramural research program is reviewed, in its entirety, by a blue ribbon panel approximately every 10 years. These panels assess and make recommendations concerning the impact of the research program, program balance, and other significant matters that play a role in the success of the program.

The IRP also benefits from targeted outside reviews using external experts that make recommendations to enhance the laboratory and clinical research environment at the NIH. In 2016, with the assistance of its Clinical Center Working Group (the "Red Team"), the Advisory Committee to the Director of NIH (ACD) recommended changes to strengthen clinical operations at the NIH.[57] This resulted in a number of changes, including the reorganization of the Clinical Center leadership structure and in improvements to the institutional review board (IRB) oversight process.

During FY 2016 to 2018, all the long-term planning activities endorsed in a separate ACD report[58] were addressed. This report includes many new ideas for ways in which the IRP supports and conducts science, making the IRP a role model for improving workforce diversity, fostering a new generation of scientists, and encouraging flexibility of support for new programs and research opportunities. As examples, The Genomic Ascertainment Cohort initiative was established to correlate human genotype and phenotype[59]; the IRP's supercomputing capacity has increased by 413 percent; a complete catalog of intramural research cores has been established and promulgated through the Collaborative Research Exchange (CREx)[60]; the Distinguished Scholars Program[61] was established in 2018 to facilitate the hiring and career development of junior-level principal investigators with a demonstrated commitment to diversity and inclusion; and the centralized Stadtman Investigator and Lasker Scholar recruitment initiatives led the way to record percentages of underrepresented minorities (10.3 percent) and women (39.2 percent) on the IRP tenure-track, as of October 1, 2018.

OIR is responsible for trans-NIH oversight and coordination of the IRP, human subject protections, animal welfare, research integrity and reproducibility, training, policy development, laboratory safety, and technology transfer conducted within NIH laboratories and clinics. OIR is led by the NIH Deputy Director for Intramural Research, and the IRP within each IC is led by a Scientific Director who helps conduct oversight. A summary of policies governing intramural research can be found in the Intramural Research Program Sourcebook.[62]

Several offices manage research training for the IRP. The Office of Intramural Training and Education is charged with helping trainees in the intramural research program (including graduate students in

[57] https://acd.od.nih.gov/documents/presentations/04212016-RedTeam.pdf.
[58] https://acd.od.nih.gov/documents/reports/ACD-IRP-WG-report.pdf.
[59] https://www.nih.gov/news-events/news-releases/nih-pilot-project-will-match-researchers-genes-gene-variants-interest.
[60] https://nih.scientist.com/upgrade.
[61] https://diversity.nih.gov/programs-partnerships/dsp.
[62] https://oir.nih.gov/sourcebook.

partnership with universities in the U.S. and abroad) to develop the scientific and professional skills needed to become independent researchers and leaders in the biomedical research community. The Office of Clinical Research Training and Medical Education covers all aspects of clinical training. In addition, most of the individual ICs have a Training Director who oversees their trainees.

NIH Clinical Center

The majority of NIH-funded clinical research takes place at teaching hospitals around the country and overseas. At any given time, however, approximately 1,600 studies are taking place at the NIH Clinical Center (CC) in Bethesda, Maryland. The CC is the world's largest hospital entirely devoted to clinical research. It is a national resource that makes it possible to rapidly translate scientific observations and laboratory discoveries into new approaches for diagnosing, treating, and preventing disease.

The NIH CC opened its doors in 1953, and the scope of NIH research expanded significantly with the opening of the Mark O. Hatfield Clinical Research Center in 2005, which houses 200 patient beds and 93 day-hospital stations. In 2018 the CC had 9,700 new patients, 4,500 inpatient admissions, and more than 95,000 outpatient visits. In addition to approximately 1,300 credentialed physicians, dentists, and postdoctoral researchers, the CC houses more than 830 nurses and 730 other allied health professionals, including pharmacists, dieticians, medical and imaging technologists, therapists, and medical records and supply staff. Since the hospital opened, it has hosted more than 510,000 clinical research participants. Because the CC is a research facility, only patients with specific and relevant kinds or stages of illness under investigation are admitted for treatment. The CC has no emergency room, and no labor and delivery services. Most patients are referred by their physicians, but approximately one-third self-refer via the Internet.

Figure 2. The NIH Clinical Center clears out the snow after the January 2016 blizzard. Regardless of the weather, the hospital maintains regular operations and is open for patients who are able to travel safely to the NIH campus. Credit: NIH.

Although the CC maintains a small portfolio of internal research programs, its primary role is to provide the necessary infrastructure for the intramural clinical research conducted by the ICs within the hospital.

This infrastructure includes the staff, facilities, systems, and resources needed for safe and high-quality patient care in support of clinical research studies.

Known as the *House of Hope* to patients, the CC has played a vital role in a long list of medical milestones, including development of chemotherapy for cancer; the first use of an immunotoxin to treat a malignancy (hairy cell leukemia); identification of the genes that cause kidney cancer, leading to the development of six new, targeted treatments for advanced kidney cancer; the demonstration that lithium helps depression; the first gene therapy; the first treatment of AIDS (with azidothymidine); and the development of tests to detect the human immunodeficiency and hepatitis viruses in blood, which led to a safer blood supply to use in clinically required blood transfusions.[63]

In 2017, the CC was the focus of *First in Human*, a Discovery Channel documentary capturing the actual experiences of doctors, researchers, staff, and patients and their caregivers at the CC as they address the challenges faced in diagnosing and treating diseases. The three-episode series showcased the innovative work that takes place at the CC, and provides an in-depth look at the reality of experimental medicine in clinical trials.[64]

The CC continues to build on its proud history of tackling the world's toughest public health challenges. For example, the CC has emerged at the forefront of addressing the Zika[65] and Ebola[66] crises. The CC's isolation facility, known as the Special Clinical Studies Unit, enables state-of-the-art care for patients with Ebola who are participating in research protocols to mitigate this deadly outbreak.

In addition to the CC on the main campus, NIH supports satellite clinical research facilities through various ICs. For example, the NIEHS Clinical Research Unit, located on the Institute's North Carolina campus, is focused on studying the interactions of genetics and environmental exposures in the development of disease. It conducts pharmacokinetic studies on environmental chemicals and studies identifying populations at increased risk for exposure to these chemicals, with the goal of developing novel preventive and therapeutic strategies to address human disease.

[63] https://clinicalcenter.nih.gov/welcome.html.
[64] https://clinicalcenter.nih.gov/ocmr/firstinhuman/index.html.
[65] https://www.niaid.nih.gov/diseases-conditions/zika-vaccines.
[66] https://clinicalcenter.nih.gov/ebola1.html.

Figure 3. Panoramic photograph of the main NIEHS building in Research Triangle Park, NC. Credit: NIEHS.

Fostering Commitment to Science

Vital to accomplishing NIH's mission to advance biomedical science and improve the health of the American people are the scientists who conduct the research. In supporting the biomedical research enterprise, NIH must not only fund the research, but also ensure that there is a robust, well-trained workforce of innovative, diverse, and dedicated researchers.[67] Furthermore, to effect real improvements in the health, findings from research must be communicated to a ready public. For these reasons, NIH invests in the recruitment, training, and retention of the research workforce and in informing the public of its scientific agenda and outcomes, supporting programs to improve science education and literacy from pre-kindergarten to adulthood.

Research Workforce Recruitment, Training, and Retention

NIH training and career development programs are designed to prepare investigators to address problems in health by using available tools and techniques, or by developing new scientific approaches, informed by the latest findings and aligned to our nation's public health challenges.

Catalog of Research Training Activities

In response to the mandate under Section 403 (a)(4)(C)(iv) of the *PHS Act* to provide a catalog of research training activities, Appendix E includes the following:

[67] NIH is mandated by the *National Research Service Award Act of 1974* (P.L. 93-348) to train researchers to meet the "nation's needs" in biomedical research.

- Funded Ruth L. Kirschstein NRSA and NLM *Institutional* Research Training Grants, FY 2016 and 2017[68]
- Funded Ruth L. Kirschstein NRSA *Individual* Fellowship Awards, FY 2016 and 2017

NIH-Wide Activities

Although NIH-wide research training and career development programs share a common goal of fostering the future research workforce, NIH ICs have the flexibility of implementing the programs to focus on specific groups of individuals, career levels, or specialized areas of research. NIH makes extra efforts to foster new investigators who focus on under-researched areas—such as clinical and translational research, rare diseases, health disparities, and global health issues—and different approaches are needed and used throughout NIH to ensure that the biomedical research workforce is up to the challenges it faces. A few of the NIH-wide research workforce recruitment, training, and retention programs are highlighted below.

An ongoing challenge is the need to balance supporting the future of the biomedical research workforce with sustaining existing research programs. NIH has long understood that supporting the future biomedical workforce is essential to cutting-edge scientific advances and lasting impact on human health needs. Over the past decade, many groups have published data on the aging of the workforce and on the age distribution of NIH-funded researchers. Since the late 1990s, the percentage of NIH-funded investigators over the age of 60 has risen significantly compared with other age groups.[69]

In renewed efforts to address the long-term stability of the biomedical research enterprise, NIH launched the NGRI in 2017.[70,71] The initiative invests in the next generation of researchers by addressing some of the challenges they face as they embark upon and sustain independent research careers by supporting their efforts to obtain a first research award and retain that support in subsequent years. The Initiative and updates to it require ICs to prioritize awards that will fund early-stage investigators and investigators with meritoriously scored applications who would not have major NIH research funding if the application under consideration is not awarded and who do not have significant research support from other sources.[72] Examples of IC initiatives that align with NGRI are covered in the subsection "IC- and Discipline-Specific Training and Career Development Activities."

Training for a career in research typically requires a combination of specialized coursework and hands-on research experiences under the guidance of an established investigator. Most NIH-funded research training activities focus on predoctoral students and postdoctoral scholars. Activities are provided either through training grants (T awards), which are awarded to institutions to support a coordinated program

[68] FY 2018 data were not available at the time this report was prepared and will be included in the next Triennial Report.
[69] NIH Advisory Committee to the Director (ACD) Next Generation Researchers Initiative Working Group. 2018. https://acd.od.nih.gov/documents/presentations/12132018NextGen_report.pdf.
[70] https://grants.nih.gov/ngri.htm.
[71] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-101.html.
[72] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-214.html.

of training for a group of students or scholars, or fellowships (F awards), which directly support an individual's training. The principal (in terms of size and breadth of coverage) NIH research training program for U.S. citizens and permanent residents is the Ruth L. Kirschstein NRSA program. The program's goal is to support promising students and postdoctoral scholars with the potential to become productive, independent investigators in fields relevant to NIH's mission. Training activities can be in basic biomedical or clinical sciences, in behavioral or social sciences, in health services research, or in any other discipline relevant to the NIH mission, and they always include instruction in the responsible conduct of research. NRSA fellowships provide recipients with valuable experience in initiating and testing their own research ideas before becoming full-fledged investigators.

Through the NIH-wide program of NRSA institutional training grants and fellowships, NIH ICs supported more than 17,683 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every state in FY 2017. Institutional training grants form the core of NIH's research training programs, providing support to more than 80 percent of all NRSA program participants. Training grants play a particularly important role at the predoctoral level: approximately 59 percent of trainees are graduate students who are often engaged in coursework and laboratory rotations in preparation for identifying an area of research for in-depth study. See Appendix E for a breakdown of the demographics of NRSA participants and a summary of the number and type of doctoral degrees awarded to predoctoral NRSA recipients.

Individuals interested in research training in universities or departments that do not offer institutional training grants, as well as advanced students and postdoctoral scholars seeking tailored training opportunities, can apply directly to NIH for individual research training fellowships.

NRSA training grants and fellowships may target broad-based or field-specific research training, depending on the needs identified by the administering IC. In recent years, this flexibility has allowed the NRSA program to accommodate interest in greater integration of training activities across NIH in order to fulfill workforce needs shared by multiple ICs. All ICs with funding authority award NRSA institutional research training grants, except FIC and NLM. Reflecting the unique nature of their missions, these two ICs have distinct training authorities separate from the NRSA program.

Examples of projects from recent NIGMS NSRA-funded trainees include the development of new methods for computational enzyme design,[73,74] investigations into species-specific barriers to transmitted HIV-1

[73] Saleem-Batcha R, et al. *Proc Natl Acad Sci USA* 2018;115(19):4909-4914. PMID: 29686059.
[74] Newmister SA, et al. *Nat Chem Biol* 2018;14(4):345-351. PMID: 29531360.

infection,[75,76] and the variation of vitamin D metabolism and regulatory genes in indigenous North American populations.[77– 84]

Some programs also serve to advance the NIH mission by encouraging students to pursue a research-oriented degree alongside another degree. To ensure a supply of investigators with expertise in research and patient care, ICs make awards for M.D./Ph.D. and other types of dual-degree training. The oldest and largest of these is the NIGMS Medical Scientist Training Program (MSTP), which provides NRSA T32 awards to medical institutions for the training of qualified M.D./Ph.D. dual-degree students who are motivated to undertake biomedical research and research-related careers in academia, industry, and government.[85] Examples of research by MSTP-funded trainees include studies developing new treatment strategies for acute myeloid leukemia, investigating the mechanism of HIV-1 replication in host cells,[86] and examining how epigenetic phenomena within immune cells modulate physiological responses to novel antigens.[87,88]

In addition to its formal research training programs, NIH supports graduate and postdoctoral research experiences through research grants. Although training on a research grant is not an NIH "program," its impact on trainees is significant. Graduate students and postdoctoral scholars acting as research assistants—often before or after an NRSA training grant appointment or fellowship—gain knowledge, skills, and experience that help prepare them for careers in research.

Given the ever-quickening pace at which science advances, investigators need opportunities to fully develop their scientific expertise and stay up to date. NIH career development awards (K awards)[89] address this need. Collectively, more than a dozen types of K awards support investigators as they establish their research careers, pursue new directions, or dedicate themselves to training and mentoring the next generation of scientists. Like the T and F training awards, some career development awards support institutional activities to nurture careers, and others directly support individual development.

Many career development awards are designed for researchers at specific career stages, particularly newly trained investigators. The NIH-wide Pathway to Independence Award[90] accelerates the transition from mentored to independent research by providing a bridging mechanism of an initial mentored period

[75] Meyerson NR, et al. *PLoS Pathog* 2018;14(3):e1006906. PMID:29518153.
[76] Meyerson NR, et al. *PLoS Pathog* 2018;14(4):e1006983. PMID: 29614111.
[77] Claw KG, et al. *Nat Commun* 2018;9(1):2957. PMID: 30054469.
[78] Wong T, et al. *Drug Metab Dispos* 2018;46(4):367-379. PMID: 29343609.
[79] Henderson LM, et al. *J Pers Med* 2018;8(1). pii: E9. PMID: 29389890.
[80] Tanner JA, et al. *Pharmacogenet Genomics* 2018;28(1):7-16. PMID: 29232328.
[81] Xu M, et al. *J Pharmacol Exp Ther* 2017 Nov;363(2):265-274. PMID: 28819071.
[82] Claw KG, et al. *Hum Bio*. 2017;89(3):177-180. PMID: 29745246.
[83] Tanner JA, et al. *J Pharmacol Exp Ther* 2017;360(1):129-139. PMID: 27815364.
[84] Chen LL, et al. *Genome Biol* 2016;17(1):210. PMID: 27729075.
[85] https://www.nigms.nih.gov/Training/InstPredoc/Pages/PredocOverview-MSTP.aspx.
[86] Stultz RD, et al. *J Virol* 2017;91(9). pii: e00034-17. PMID: 28250118.
[87] Lau CM, et al. *Nat Immunol* 2018;19(9):963-972. PMID: 30082830.
[88] Okoye-Okafor UC, et al. *Nat Chem Biol* 2015;11(11):878-86. PMID: 26436839.
[89] http://grants.nih.gov/training/careerdevelopmentawards.htm.
[90] http://grants1.nih.gov/grants/guide/pa-files/PA-11-197.html.

of 1 to 2 years, followed by an independent phase during which awardees establish their own research programs and apply for independent research support. Other mentored career development awards provide support for a sustained period of protected time for intensive research career development under the guidance of an experienced investigator. The expectation is that, with this experience, awardees will be able to take the final steps toward establishing independent research careers and becoming competitive for new research project grant funding. At the other end of the career spectrum, a number of ICs provide career development opportunities to mid-career and established investigators. These awards provide salary support for outstanding senior scientists and recognized leaders so they can focus intensively on their research and mentor new investigators.

The NIH Loan Repayment Programs are another key component of NIH's efforts to attract eligible doctoral-level professionals to careers in biomedical research.[91] The Loan Repayment Programs provide financial assistance for educational debt in exchange for a 1- to 3-year research commitment, depending on the program. More than 1,600 program participants each year receive up to $50,000 annually in loan repayment and fulfill their commitments by conducting research in nonprofit, university, or government settings. An evaluation of the program showed that, compared to their peers, participants in the program stay in research careers longer, apply for and receive more research grants, and are more likely to become independent investigators.[92]

To coordinate research training and career development across the NIH, OER partners with ICs to coordinate a consistent view of training awards—whether the IC requires an examination of its implementation of policies and guidelines, profiles of workforce needs, large-scale data gathering and evaluation efforts, development of trans-NIH initiatives, or maintenance of information systems to support all of the above.[93] To facilitate information sharing, the identification and discussion of issues, and the coordination of activities across NIH, OER also convenes monthly meetings of the NIH Training Advisory Committee. Made up of representatives from each of the 27 ICs, the committee is an agency-wide forum for issues related to research training.[94]

IC- and Discipline-Specific Activities

Every IC and many OD offices support training programs specific to their mission. For example, the Clinical and Translational Science Awards (CTSAs) administered by NCATS provide research training and career development opportunities in such areas as clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, behavioral science, and ethics. In 2017, there were 923 NRSA trainees and new investigators, and data on CTSA trainees are included in the NRSA data provided in Appendix E. In 2018, NCATS' CTSA and NIDCR announced a collaboration to provide translational research training opportunities to oral, dental, and craniofacial scientists early in their careers. Through supplemental funding to CTSA's Mentored Career Development Awards, the program supports career

[91] https://www.lrp.nih.gov/.
[92] https://www.lrp.nih.gov/sites/default/files/docs/pdfs/LRP-Flyer-Final-Updated-6-3-2019.pdf.
[93] https://researchtraining.nih.gov/.
[94] https://researchtraining.nih.gov/tac-roster.

development of five investigators conducting research in oral, dental, and craniofacial disease and prevention.[95]

To gain a broader understanding of what research may mean and illustrate the range of careers that are possible within research, training programs also call upon a variety of stakeholders for partnership. The NCATS CTSA externship program pairs CTSA Program scholars and trainees with a mentor at the pharmaceutical company Eli Lilly, where they are fully embedded in a project team. Now in its third year, the NCATS Lilly externship program is intended to enhance translational scientists' skills in areas critical to the drug development process, from clinical trial design and disease modeling to regulatory issues and how to work with the FDA.[96]

Medical research breakthroughs take an average of 17 years to enter routine clinical practice, and additional barriers often cause further delays for medically underserved populations. This length of time means that proven knowledge about preventive, acute, and long-term care will be delayed or may never be delivered in the care and medical advice that many Americans receive. Implementation research can address the lag of effective interventions in medical practice by identifying strategies to accelerate the sustainable adoption of discoveries and to weed out ineffective practices in real-world settings. In 2017, NHLBI funded 10 new training programs at institutions across the country to help build and foster a sustainable, diverse, and properly trained workforce in implementation science.[97]

NHLBI, NCI, NIAID, and NIA participated in the Stimulating Access to Research in Residency (StARR) program, which was initiated and launched by OER in 2018 specifically to bring more physician-scientists into the research workforce. NLHBI made awards to seven institutions to support tools, mentorship, training, and funding needed to accelerate the entry of medical residents into meaningful research pursuits. For example, one StARR grant is focused on training pediatric residents to pursue careers in heart, lung, and blood research.[98]

NIMH also supports exceptional early investigators through the NIMH Biobehavioral Research Awards for Innovative New Scientists (BRAINS) program.[99] BRAINS supports the research and research career advancement of outstanding, exceptionally productive scientists who are in the early, formative stages of their careers and who plan to make a long-term career commitment to research in specific mission areas of NIMH. This award assists individuals in launching an innovative clinical, translational, basic, or services research program that holds the potential to profoundly transform the understanding, diagnosis, treatment, or prevention of mental disorders.

The Predoctoral Training in Advanced Data Analytics for Behavioral and Social Sciences Research (BSSR)–Institutional Research Training Program opportunity, an OBSSR-led institutional NRSA (T32), supports the development of a cohort of specialized predoctoral trainees who will be trained in advanced data science

[95] https://ncats.nih.gov/pubs/features/nidcr.
[96] https://ncats.nih.gov/pubs/features/eli-lilly-2018.
[97] https://www.nhlbi.nih.gov/news/2017/building-workforce-translate-discoveries-health.
[98] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-023.html.
[99] https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-18-200.html.

analysis and its application to an increasingly complex landscape of big data related to behavioral and social science. The training includes various aspects of computer science/informatics and statistics/mathematics that are directly relevant to behavioral and social science research in health, and it provides quantitatively minded students important context for properly interpreting findings in the new data-rich environment.[100]

The Big Data to Knowledge (BD2K) program, launched in 2012, continues to support formal research training and career development programs, as well as short courses, research experiences, and the development of new curricula and other educational resources for data science.[101] In March 2017, the BD2K Training Program Management Working Group reported on investments made during prior years that indicated that training accounted for approximately 15 percent of the budget for the BD2K Initiative, with FY 2016 expenditures of nearly $17 million for new and continuing awards.[102]

Other components within the Office of the NIH Director coordinate specialized training and related awards, as well as opportunities for newly independent investigators. For example, the NIH Common Fund's Early Independence Awards provide outstanding junior scientists who have the intellect, scientific creativity, drive, and maturity an opportunity to forgo the traditional period of postdoctoral training entirely and pursue their own program of independent research.[103] Past awardees have focused on such topics as development of language skills in infants and bioengineering solutions to supplement scarce antibodies essential for conducting research on protein structure.[104]

In addition, ODP launched an Early Stage Investigator Lecture award to recognize early-career prevention scientists who have not successfully competed for an R01 or R01-equivalent NIH research grant but who have made significant research contributions to their respective fields and are poised to become future leaders in prevention research. Award priority is given to nominees conducting applied prevention research on any of the following common risk factors for death and disability in the U.S.: tobacco, overweight/obesity, poor diet, physical inactivity, alcohol misuse, substance misuse, risky sexual behavior, injury and violence, infectious disease, and environmental health. ODP also considers nominations in the areas of reducing health disparities, advancing research on methods and measurement, and screening for disease. The award winner is invited to give a lecture at NIH and is offered an opportunity for professional networking with NIH program directors and scientists during a 2-day visit.[105]

To encourage the application of innovative methods and enhance the research capabilities of investigators conducting health-relevant behavioral and social sciences research, OBSSR supports a variety of online and in-person training experiences in collaboration with the U.S. Department of Veterans

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[100] https://grants.nih.gov/grants/guide/rfa-files/rfa-od-19-011.html.
[101] https://commonfund.nih.gov/bd2k.
[102] BD2K Training Program Management Working Group. *Annual Report on Investments in Training and Education for the NIH Big Data to Knowledge (BD2K) Initiative.* 2017. https://commonfund.nih.gov/sites/default/files/AnnualReportOnInvestmentsInTrainingAndEducationForBD2K_FY1416_508.pdf.
[103] http://commonfund.nih.gov/earlyindependence.
[104] https://commonfund.nih.gov/earlyindependence/programhighlights.
[105] https://prevention.nih.gov/news-events/early-stage-investigator-lecture.

Affairs (VA), FIC, NCI, NINR, NIAAA, NHLBI, NIMH, NIDA, NCCIH, and NIDDK. For example, the Training Institute on Dissemination and Implementation Research in Health provides participants with a thorough grounding in conducting dissemination and implementation (D&I) research across all areas of health and health care. The science of D&I seeks to address the gap between what is known to optimize health and what actually gets implemented in everyday practice by understanding how best to ensure that evidence-based strategies to improve health and prevent disease are effectively delivered in clinical and public health practice.[106]

NIH's Basic Behavioral and Social Sciences Opportunity Network (OppNet), coordinated by OBSSR, supports Research Career Enhancement (K18) awards to allow established investigators to gain knowledge in fields outside of their primary discipline, expand their expertise, and facilitate collaboration in important new directions. OBSSR assessed how the unique features of K18 awards affect the ability of recipients to obtain follow-on NIH research funding and found that OppNet K18 award recipients were as successful as other K award recipients in obtaining follow-on funding, with each K18 award requiring less investment per investigator than other K awards.[107,108]

OBSSR also coordinates the R25 research education program, *Short Courses on Innovative Methodologies in Behavioral and Social Sciences*. These courses provide training for skills development in crosscutting methodologies and analytics that are needed to advance behavioral and social sciences research and were supported by NICHD, NIDA, NIEHS, NIMH, NCCIH, NHLBI, and NIDDK. Methodological domains of focus include, but are not limited to, innovative data collection methodologies and analytic techniques, analysis and linking of big data, and novel study designs to advance research across the translational spectrum. The goal is for the short courses to build capacity in the field and encourage future incorporation of new and innovative methods and models within the behavioral and social sciences fields.[109]

In collaboration with the National Science Foundation (NSF), OBSSR sponsored *Graduate Training in the Social and Behavioral Sciences: A Public Workshop at the National Academies of Science* to identify educational changes needed to better prepare Ph.D. students in the social and behavioral sciences. The Board on Science Education convened the 2-day workshop in June 2017, which included current social and behavioral sciences graduate students, postdoctoral fellows, faculty and academic leaders, members of professional societies, funding agencies, and leaders in government and business. The proceedings, published in 2017, informed stakeholders about potential ways to transform training and career pathways in response to changing data resources, research practices, and career opportunities.[110,111]

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[106] https://www.scgcorp.com/tidirh2018/index.html.
[107] Pomeroy-Carter CA, et al. *PLoS One* 2018;13(2):e0192543. PMID: 29438411.
[108] https://oppnet.nih.gov/.
[109] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-012.html.
[110] National Academies of Sciences, Engineering, and Medicine. 2017. Graduate Training in the Social and Behavioral Sciences: Proceedings of a Workshop—in Brief. Washington, DC: The National Academies Press. https://doi.org/10.17226/24891.
[111] https://sites.nationalacademies.org/DBASSE/BOSE/CurrentProjects/DBASSE_175769.

NIH also partners with other federal agencies to enhance training opportunities. The Veterans Health Administration (VHA)–NCI Big Data Scientist Training Enhancement Program (BD-STEP), which was co-launched by VHA and NCI in FY 2016, embeds postdoctoral scientists and engineers in VA medical centers to apply quantitative techniques to challenges in clinical oncology. Initially, 26 fellows participated over three cohorts, and they are now employed by the VA or industry, have continued in their academic roles, or have returned for a second year of the program. A fourth cohort of 16 fellows was enrolled in 2018.[112]

A number of programs across ICs align with the NGRI, described previously under NIH-Wide Activities. For example, NIGMS launched the Maximizing Investigator Research Award (MIRA) R35 program, with its first awards made in FY 2016. The goal of MIRA is to increase the efficiency of NIGMS funding by providing investigators with greater stability and flexibility, thereby enhancing scientific productivity and the chances for important breakthroughs. The program also will help to distribute funding more widely among the nation's highly talented and promising investigators. Over three years, from FY 2016 to 2018, NIGMS made 651 new awards to both established and early-stage investigators through this new program. The Early Stage Investigator MIRA program, in particular, has encouraged applications from investigators at earlier stages in their careers and has contributed to meeting the NIH-wide goals of supporting early-stage investigators as part of the NGRI.[113]

Similarly, NINDS also has recently begun to use the R35 research grant mechanism to provide funding stability that enables even greater innovation in the laboratories of investigators who have a proven track record and a proposal judged to have outstanding potential by a peer review committee. In exchange for an award that supports NINDS mission-relevant research for up to 8 years, R35 investigators must commit at least 50 percent effort to overseeing the research program. The goal is to enable a cohort of investigators to spend more time devoting their creativity to the pursuit of cutting-edge science.[114]

The NIAMS Supplements to Advance Research (STAR) award program supports NIAMS investigators who recently renewed their first major independent award as they work to expand their research from a single, structured project into a broader, multifaceted research program. Reflecting NIAMS' commitment to early-career investigators, the STAR program aligns with the trans-NIH NGRI.[115]

NHLBI launched a new program in 2016 to provide researchers the flexibility and support they need to conduct innovative high-risk research while providing an accelerated path for early-stage investigators to become tomorrow's scientific leaders. To that end, NHLBI's Emerging Investigator and Outstanding Investigator Awards program provides up to 7 years of funding, which lessens the administrative burden on the investigators by reducing the time they have to spend preparing multiple grant submissions. Thus,

[112] https://www.va.gov/oaa/specialfellows/programs/sf_bdstep.asp.
[113] https://www.nigms.nih.gov/research/mechanisms/mira/pages/default.aspx.
[114] https://www.ninds.nih.gov/News-Events/Directors-Messages/All-Directors-Messages/NINDS-R35-Program-innovation-experiment.
[115] https://www.niams.nih.gov/grants-funding/funded-research/supplements-advance-research-star.

the program provides a nimbler platform for pursuing scientific opportunities. NHLBI made 39 awards in the first year of funding and expects to make more new awards in upcoming years.[116]

The Trailblazer R21 Award is an opportunity for new and early-stage investigators to pursue research programs of high interest to NIBIB at the interface of the life sciences with engineering and the physical sciences. The program employs an R21 Exploratory/Developmental Research Grant mechanism, enhanced to provide $400,000 in direct costs over 3 years, allowing sufficient time and resources to pursue a new or emerging research program.[117]

Recognizing the need to support the next generation of investigators, NIDA established the Avenir Award Program in 2014. Meaning *future* in French, this award supports early-stage investigators proposing highly innovative studies, focused on both HIV/AIDS genetics and the genetics and epigenetics of addiction. NIDA funded six recipients in 2018, seven in 2017, and seven in 2016, investigating questions ranging from the social networks of injection drug users with HIV, to understanding genetic risk factors for addiction, to identifying the epigenetic changes that occur in association with addiction.[118]

NIDA also supports the NIDA Diversity Scholar Network, a rigorous and comprehensive mentorship program to improve the funding of outstanding early-stage investigators from diverse backgrounds, including from underrepresented groups, in substance misuse research. The program consists of two separate meetings with an interim application development period to assist scholars in applying for and receiving NIH career development awards and research grants. Scholars will be paired with an experienced scientist throughout this process.[119]

Additional programs provide support even earlier in a career, when trainees are working toward obtaining their degree. For example, NCI's Predoctoral to Postdoctoral Fellow Transition Award (F99/K00) offers outstanding graduate students an early start to a career path as an independent researcher. It provides late-stage predoctoral students with funding to complete their dissertation (F99), followed by a transition to 4 years of cancer-focused postdoctoral training at a U.S.-based institution (K00).[120,121] Initially developed by NCI, the F99/K00 award program is now being adopted by other NIH ICs.

NIH also recognizes that traditional research-intensive positions are only one means by which individuals may contribute to the biomedical research enterprise. The NIH Common Fund's Strengthening the Biomedical Research Workforce program aims to enhance training opportunities for early-career scientists to prepare them for a variety of career options in biomedical research. This program supported Broadening Experiences in Scientific Training (BEST) awards to academic institutions for the development of innovative approaches to complement traditional research training, such as professional skills

[116] https://grants.nih.gov/grants/guide/rfa-files/rfa-hl-16-025.html.
[117] https://www.nibib.nih.gov/research-funding/trailblazer-r21-awards.
[118] https://www.drugabuse.gov/news-events/avenir-award-winners.
[119] https://www.drugabuse.gov/offices/office-nida-director-od/office-diversity-health-disparities-odhd/odhd-research-training-programs/nida-diversity-scholars-network-ndsn.
[120] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-18-001.html.
[121] https://www.cancer.gov/grants-training/training/funding/f99.

development, internships, and peer and alumni networking. In 2017, the NIH BEST Consortium reported on lessons learned from the BEST programs and practical guidance on how to motivate, create, implement, and evaluate career and professional development opportunities for doctoral and postdoctoral scholars.

The NINR Boot Camp is a 1-week intensive research training course at NIH in Bethesda, Maryland. Sponsored by NINR, the course is administered by the Foundation for Advanced Education in the Sciences. In 2016 and 2017, the Boot Camp presented *Precision Health: From "Omics" to Data Science,* and in 2018, *Precision Health: Smart Technologies, Smart Health*.[122]

Similarly, the Summer Genetics Institute is a tuition-free 1-month intensive research training program at NIH, also sponsored by NINR. Participants are provided with a foundation in molecular genetics appropriate for use in research and clinical practice. The program, featuring both lectures and hands-on laboratory training, seeks to increase the research capability among graduate students and faculty and to develop and expand clinical practice in genetics among clinicians. More than 300 institute graduates are making a difference in communities across the country by building programs of nursing research in genetics, disseminating the results of genetics-related research in peer-reviewed scientific publications and at scientific conferences, and integrating genetics content in nursing school curricula and practice.[123]

NLM's training programs support short-term summer research experiences, which were expanded in FY 2018 to support nearly 40 graduate and undergraduate students. NLM funded six career awards in FY 2018 from two career transition programs that are offered to NLM trainees and others ready to launch informatics research careers; NLM also offered administrative supplements to existing NIH research grantees who want to add an information specialist to their research team. This last component is particularly critical, because information specialists help ensure that research teams follow best practices for collecting, managing, and analyzing data in ways that facilitate and support rigorous and reproducible research. Taken together, NLM's commitment to training and career transition in FY 2018 represented more than 30 percent of NLM's extramural grants budget.[124]

Aside from hands-on experience, other aspects of training are also important—not the least of which is mentorship. In recognition of the contribution of mentors, NINDS selects up to five recipients for the Landis Award for Outstanding Mentorship each year from among faculty members who have shown dedication to superior mentorship and training in neuroscience research. NINDS hopes this tangible award will impress upon the scientific community as a whole—and faculty and institutional leaders, in particular—the high value NINDS places on training and mentorship and the need to recognize and encourage dedication to mentorship in addition to outstanding research accomplishments.[125]

[122] https://www.ninr.nih.gov/training/trainingopportunitiesintramural/bootcamp.
[123] https://www.ninr.nih.gov/training/trainingopportunitiesintramural/summergeneticsinstitute.
[124] https://www.nlm.nih.gov/ep/Grants.html#training.
[125] https://www.ninds.nih.gov/Funding/About-Funding/landis-award-for-outstanding-mentorship.

Biomedical Workforce Diversity

The diversity of research training participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Of the FY 2017 trainees and fellows who reported their race and ethnicity, 63.2 percent were White, 16.0 percent were Asian, 7.2 percent were African American, 12.6 percent were Hispanic, 0.6 percent were Native American, 0.2 percent were Native Hawaiian or Other Pacific Islander, and 4.6 percent were multiracial. More than 53 percent of trainees and fellows in FY 2017 were women.

Across NIH, NRSA training grants and fellowships help promote research training opportunities for individuals from diverse backgrounds, including those from populations and backgrounds typically underrepresented in research. At the graduate and postdoctoral levels, NIH policy requires institutional training grant directors to take steps to recruit a diverse pool of candidates for training programs from underrepresented groups, including racial and ethnic minorities and individuals with disabilities. Through the Ruth L. Kirschstein NRSA for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research, NIH also provides graduate students from diverse backgrounds, including those from underrepresented groups, with opportunities to pursue research training through individual fellowship awards.[126] Because recruiting talented individuals into research training programs requires a pool of prepared applicants from which to draw, NIH offers undergraduate research training to honors students at selected institutions who are interested in a research career and who intend to pursue postgraduate education leading to a Ph.D., M.D./Ph.D., or other combined research degree.

ICOs also have continued programming in alignment with NIH's workforce diversity goals. Some programs are described below, with additional programs included in the section of Chapter 3 titled Minority Health and Health Disparities.

NIMHD's Mentored Career Development Awards program aims to enhance the pool of highly trained new investigators from diverse backgrounds, including those who are underrepresented in research areas of interest to NIMHD, and encourages these postdoctoral scholars to pursue research independence. In FY 2018, NIMHD funded 10 new projects focused on such areas as developing research skills in cardiometabolic health in racial and ethnic minority youth and African American breast cancer survivors; epigenetic mechanisms of prenatal environmental stressors and offspring obesity risk; mobile health interventions to reduce diabetes disparities in Chinese Americans; social media use to address depression outcomes among U.S. lesbian, gay, and bisexual young adults; and precarious employment as a determinant of overweight and cardiometabolic risk.[127]

The NIH Sexual and Gender Minority (SGM) Investigator Award Program was developed to recognize early- and mid-career investigators who have made substantial, outstanding research contributions in areas related to SGM health and who are poised to become or already are leaders in the field of SGM

[126] https://researchtraining.nih.gov/programs/fellowships/f31#.
[127] https://www.nimhd.nih.gov/programs/extramural/training-career-dev/career-dev-awards.html.

health research. Two awards were made in 2018 as part of the inaugural event. Presentation of the awards will be an annual event for the SGM research community.[128]

In 2000, ORWH created its institutional career development grant program, Building Interdisciplinary Research Careers in Women's Health (BIRCWH), designed to expand the numbers and expertise of junior faculty. BIRCWH supports Scholars in successfully pursuing research careers relevant to the health of women and, where appropriate, the inclusion of both sexes in studies to better understand the influence of sex as a biological variable on health and disease. Since its inception, the 20 active BIRCWH grant programs have provided mentored research career development to more than 700 Scholars in the areas of interdisciplinary basic, translational, behavioral, clinical, and/or health services research with support from NCI, NIA, NIAID, NIAMS, NIDA, NIDCR, and NIMH, with NICHD serving as a co-funder and the administrative institute for the program.[129]

The NIGMS Initiative for Maximizing Student Development Program awards provide support to educational activities to complement and enhance the training of a workforce to meet the nation's biomedical, behavioral, and clinical research needs[130] by providing short-term research experiences and courses for skills development. Examples of research that participants led and contributed to include studies to investigate the role of a metal transporter in oligodendrocyte maturation and myelination,[131] to understand gene regulation and function using genome-wide methods,[132] and to identify biomarkers for osteosarcoma to help monitor tumor burden, detect early relapses, and predict prognosis.[133]

The NIGMS Maximizing Access to Research Careers (MARC) Undergraduate Student Training in Academic Research (U-STAR) awards provide support for undergraduate students from diverse backgrounds, including those from groups underrepresented in the biomedical sciences, to improve their preparation for high-caliber graduate training at the Ph.D. level.[134] Examples of research that trainees led and contributed to include studies to elucidate the detergent–lipid–protein interactions of solubilized membrane proteins,[135] to identify genome-wide signals responsible for the early induction of the body axis,[136] and to investigate the mechanisms that regulate cyclin-dependent kinases in cell cycle and transcription.[137]

Within the field of genomics, NHGRI expanded its Diversity Action Plan initiative beyond programs already affiliated with NHGRI from closed-competition to open-competition, allowing all proposals within the scientific mission of NHGRI to be eligible for funding under the program. The program aims to train a

[128] https://dpcpsi.nih.gov/sgmro/events/research-investigator-awards-2018.
[129] https://orwh.od.nih.gov/career-development/building-interdisciplinary-research-careers-womens-health-bircwh.
[130] https://www.nigms.nih.gov/training/IMSD.
[131] Cheli VT, et al. *J Neurosci* 2018;38(43):9142-9159. PMID: 30190412.
[132] Byrne A, et al. *Nat Commun* 2017;8:16027. PMID: 28722025.
[133] Nakka M, et al. *Oncotarget* 2017;8(57):96738-96752. PMID: 29228567.
[134] https://www.nigms.nih.gov/Training/MARC/Pages/USTARAwards.aspx.
[135] Quesada O, et al. *Sci Rep* 2016;6:32766. PMID: 27641515.
[136] Ding Y, et al. *Proc Natl Acad Sci USA* 2017;114(15):E3081-E3090. PMID: 28348214.
[137] Roach BL, et al. *Biochem Biophys Res Commun* 2018;504(4):753-758. PMID: 30217452.

diverse group of scientists to pursue research in the fields of genomics and/or ethical, legal, and social issues research.[138]

NCI supports the Nursing Postdoctoral Program in Cancer and Health Disparities. This program focuses on developing a diverse and highly trained workforce of nursing faculty and researchers committed to better understand and address cancer health disparities. It is the only nursing postdoctoral program co-developed by any college or school of nursing and a clinical partner.[139,140]

Cultivating the next generation of leading informaticians and fostering the diverse perspectives that support leading research requires active outreach to underrepresented and disadvantaged groups at earlier educational stages. In FY 2018, NLM offered supplemental funds to support partnerships with institutions that have a track record of training students from underrepresented groups. Three such supplements were awarded to help facilitate recruitment of high school and undergraduate students into biomedical informatics training programs. To enhance outreach, these supplements emphasized the presentation of student work to bring greater awareness of biomedical informatics and data science literacy to a greater number of diverse young scholars.[141]

NHLBI's ongoing Programs to Increase Diversity among Individuals Engaged in Health-Related Research (PRIDE) initiative aims to broaden the demographic profile of biomedical research by enhancing the research skills of postdoctoral students and junior faculty from diverse backgrounds, including those from underrepresented racial and ethnic groups and those with disabilities. The PRIDE initiative supports summer institutes in which each participant is paired with an experienced scientist with shared research interests to build a sustainable independent career that will help meet the nation's future needs in heart, lung, blood, and sleep research. An evaluation of PRIDE and its predecessor program published in 2017 found increased publications, grants, promotion, and tenure rates among participants, as well as attainment of important manuscript and grantsmanship skills.[142,143]

Since 2016, NIMHD has hosted the Health Disparities Research Institute, which aims to support the research career development of promising minority health/health disparities research scientists early in their careers and stimulate research in the disciplines supported by health disparities science. This program is intended for early-stage investigators at the senior postdoctoral or early assistant professor level. Applicants must have a Ph.D., M.D./D.O., Sc.D., Dr.P.H., Pharm.D., Psy.D., or equivalent doctoral

[138] https://www.genome.gov/14514228/history-of-nhgris-minoritydiversity-action-plan/.
[139] Gombos F, et al. *Arch Stomatol* 1989;30(5):937-59. PMID: 2577119.
[140] University of Massachusetts Boston – Dana-Farber/Harvard Cancer Center U54 Comprehensive Partnership for Cancer Disparities Research. *Post-Doctoral Nursing Fellowship in Cancer and Health Disparities.* 2017. http://www.dfhcc.harvard.edu/fileadmin/media/IECD/U54_Nursing_Post-Doctoral_Fellowship_-_2017.pdf.
[141] https://www.nlm.nih.gov/ep/Grants.html#training.
[142] Rice TK, et al. *Ethn Dis* 2017;27(3):249-256. PMID: 28811736.
[143] https://www.nhlbi.nih.gov/node-general/programs-increase-diversity-among-individuals-engaged-health-related-research-pride.

degree from an accredited domestic or foreign institution and have the intent to write a competitive grant application in the following year.[144]

The NIMHD Minority Health and Health Disparities Research Training program supports research training activities in minority health and health disparities research for individuals from diverse backgrounds, including groups underrepresented in biomedical, behavioral, clinical, and social sciences research at domestic institutions and/or at specified foreign low- and middle-income locations. The program promotes both domestic and international training opportunities in a diverse and inclusive environment for eligible undergraduate, postbaccalaureate, and graduate students, as well as for eligible residents, fellows, and pre- and postdoctoral students. Its goals are to help establish a diverse pool of highly trained scientists in appropriate scientific disciplines to address the nation's biomedical, behavioral, clinical, and social sciences research needs and to advance scientific research to improve minority health and reduce health disparities.[145]

The NIMHD Clinical Research Education and Career Development awards help institutions with a track record of training students from underrepresented groups develop and implement curriculum-dependent degree programs to train doctoral and postdoctoral candidates in clinical research. The awards are also supported by NIAMS, NIA, and NIDA and provide didactic training and mentored clinical research experiences to early-career investigators. The Clinical Research Education and Career Development awards aim to support creative and innovative research education programs that promote the development of well-trained clinical researchers who can lead clinical and translational research. Supported programs must lead to a Master of Science degree in clinical research or a Master of Public Health degree in a clinically relevant area. The overarching goals are to expand the national capability for research in clinical and translational sciences and develop a diverse group of clinical researchers who have the necessary knowledge and skills to pursue clinical, translational, and patient-oriented research on diseases that disproportionately affect racial and ethnic minority populations.[146]

The Diversity Program Consortium is composed of three complementary components to develop, implement, assess, and disseminate effective approaches to enhance the participation and persistence of individuals from diverse backgrounds, including those from groups underrepresented in biomedical research. These include (1) developing and disseminating approaches for engaging, training, and mentoring students; (2) enhancing faculty development; and (3) strengthening institutional research training infrastructure. Supported by the NIH Common Fund, managed by NIGMS, and launched in FY 2014, this program includes the National Research Mentoring Network, which is a national network of mentors and mentees from all biomedical disciplines relevant to the NIH mission. This network provides mentorship, professional development, mentor/mentee training, networking, and resources to individuals from the undergraduate to early-career faculty levels.[147]

[144] https://www.nimhd.nih.gov/programs/edu-training/hd-research-institute/hdri_logon.asp.
[145] https://www.nimhd.nih.gov/programs/extramural/domestic-international-research-training.html.
[146] https://www.nimhd.nih.gov/programs/extramural/research-centers/rcmi/crecd.html.
[147] https://www.nigms.nih.gov/training/dpc/Pages/default.aspx.

Hispanic/Latino populations in the U.S. currently bear a disproportionate burden of the HIV/AIDS epidemic. *Adelante* means forward/onward in Spanish, and the goal of the Adelante program is to decrease HIV-related health disparities in the Hispanic/Latino community by promoting the mentored development of new investigators who are focusing on this goal. To accomplish this, OAR supported three-person Adelante teams to conduct 2-year mentored Community Based Participatory Research projects. Adelante teams consists of an early-career university-based faculty member, a staff member from a community-based organization serving Latino/Hispanic populations, and a senior faculty member affiliated with the Centers for AIDS Research (CFAR). This program was started in 2015 and is facilitated by OAR in partnership with NIAID and CFAR. In 2018, NIMHD became the lead Institute for the effort with dedicated funding from OAR.[148]

Part of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative, co-led by NINDS and NIMH, the NIH BRAIN Initiative Advanced Postdoctoral Career Transition Award to Promote Diversity (K99/R00) program is designed to enhance workforce diversity in the neuroscience workforce and maintain a strong cohort of new and talented, NIH-supported, independent investigators from diverse backgrounds (including women, individuals from underrepresented racial and ethnic groups, and individuals with disabilities), in BRAIN Initiative research careers in BRAIN Initiative research areas. This program is designed to facilitate a timely transition of outstanding postdoctoral researchers with a research and/or clinical doctorate degree from mentored, postdoctoral research positions to independent, tenure-track or equivalent faculty positions. The program will provide independent NIH research support during this transition to help awardees launch competitive, independent research careers.[149,150]

The NIH Blueprint Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (BP-ENDURE) program offers opportunities in neuroscience research for individuals from diverse backgrounds, including those from underrepresented racial and ethnic groups, individuals with disabilities, and those at economic disadvantage.[151] The NIH Blueprint for Neuroscience Research program, a cooperative effort among 17 ICOs, has provided training opportunities for undergraduate and graduate students in integrated neuroscience since 2004. The BP-ENDURE program engages undergraduates from diverse backgrounds, including those from underrepresented groups, in a 2-year neuroscience research program during the academic and summer months, starting in their sophomore or junior year, for an average of 1,700 research hours upon completion of the program.[152]

NIEHS' Scholars Connect Program is a research training internship that lasts for one academic year (summer, fall, and spring semesters) for local undergraduate students from diverse backgrounds, including those from underrepresented groups. The internship also includes mentoring, career and

[148] http://www.cfar-adelante.org/faq/.
[149] https://grants.nih.gov/grants/guide/pa-files/PAR-18-814.html.
[150] https://grants.nih.gov/grants/guide/pa-files/PAR-18-813.html.
[151] https://neuroscienceblueprint.nih.gov/endure-undergraduate-education.
[152] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-14-010.html.

professional development seminars and workshops, and presentation opportunities. The program includes up to 10 students per cohort with 49 students enrolled in total as of FY 2018.[153]

A regional training hub partnership located in the Yakama Nation Reservation in Yakima, Washington, facilitated by OD THRO and NINDS prepares high school students from diverse backgrounds, including those from underrepresented groups to be competitive applicants for the NIH Summer Intern Program. The objective of this 8-week program is to expose diverse students at local academic institutions to basic laboratory procedures, including planning experiments, evaluating data, keeping a laboratory notebook, reading and evaluating journal articles, and understanding basic laboratory techniques. Regional training hubs have been a very successful model and NIH is expanding this program to other tribal communities across the country.

International Workforce Programs

NIH works to expand capacity for research internationally, particularly in low- and middle-income countries (LMICs). For example, the Fogarty Emerging Global Leader Career Development Award—with support and collaboration from NCI, NHGRI, NIDCR, NIEHS, NIMH, and NINDS—provides research support and protected time to a scientist who holds an academic junior faculty position or research scientist appointment at an LMIC academic or research institution.[154]

Programs also focus on areas particularly pertinent to the host countries. In 2018, FIC announced a funding opportunity with NHGRI focused on supporting International Bioethics Research Training. The overall goal of this program is to contribute to the development of a sustainable critical mass of bioethics leaders at the LMIC research-intensive institution to meet the needs for research ethics capacity in participating countries.[155] Before that, FIC and NHGRI published a 2016 review: *Bioethics training programmes for Africa: evaluating professional and bioethics-related achievements of African trainees after a decade of Fogarty NIH investment,* which found that trainees were significantly more likely to report higher levels of professional achievement after training.[156]

In 2016, in collaboration with ORWH and NICHD, FIC funded eight new awards focused on strengthening injury and trauma research capacity in Afghanistan, Armenia, Botswana, Egypt, Ethiopia, Pakistan, Georgia, Ghana, Moldova, Nigeria, Romania, South Africa, Sudan, and Vietnam. These projects focused on creating long-, medium-, and short-term training in various trauma and injury priority areas that are currently underdeveloped at a given LMIC institution, including physical and psychological trauma and injury.[157]

The Non-Communicable Diseases and Disorders Across the Lifespan program supports institutional research training awards for training programs designed to strengthen the capacity of institutions in LMICs

[153] https://www.niehs.nih.gov/careers/research/scholars/index.cfm.
[154] https://www.fic.nih.gov/Programs/Pages/emerging-global-leader.aspx.
[155] https://grants.nih.gov/grants/guide/pa-files/PAR-18-716.html.
[156] Kass NE, et al. *BMJ Open* 2016;6(9):e012758. PMID: 27633644.
[157] https://grants.nih.gov/grants/guide/rfa-files/RFA-TW-16-001.html.

to support independent research through the educational and career development of individual researchers and key personnel. The trainees are expected to contribute to the research capacity in their LMICs upon completion of their training and are funded through FIC, NCCIH, NIA, NIDCR, NIEHS, NIMH, and NINDS.[158]

The GEOHealth network aims to strengthen environmental and occupational health–related research collaborations internationally. It accelerates scientific infrastructure development, enhances research training, and creates relevant advanced educational curricula and outreach material to support research addressing environmental and occupational exposures to inform nationally relevant policy development in LMICs. This program links an LMIC institution for research with a U.S. institution to coordinate research training and has involved NIEHS, FIC, NCI, National Institute for Occupational Safety and Health (NIOSH), and Canada's International Development Research Centre.[159]

The International Summit in Human Genetics and Genomics is a 5-year initiative was launched in FY 2016 to build capacity in genomic research and medical genetics in developing countries. The purpose of the Summit is to strengthen cooperation among countries and reduce global health disparities, because many LMICs do not have an adequate workforce to address the burden of genetic diseases. Every year, NHGRI invites health care professionals and researchers from around the world to apply to attend the Summit, which is a month-long training session at the NIH that includes coursework, field visits, and hands-on training.[160]

To strengthen HIV/AIDS research training in LMICs, Fogarty-funded HIV/AIDS training programs in Ethiopia, Haiti, Malawi, South Africa, Zambia, and Zimbabwe received supplements of more than $700,000 to fund mentoring and leadership activities.[161]

The Human Heredity and Health in Africa (H3Africa) Initiative is a partnership between NIH, the African Society of Human Genetics, and the Wellcome Trust through the Alliance for Accelerating Science in Africa. The H3Africa consortium facilitates fundamental research into diseases on the African continent while also developing infrastructure, resources, training, and ethical guidelines to support a sustainable African research enterprise that is led by African scientists, for the African people.[162]

In response to the need for bioinformatics research leadership and sustainable training capacity in African institutions, the NIH Common Fund, NHGRI, and FIC launched a bioinformatics research training program as a new component to the H3Africa consortium. Bioinformatics degree programs will be established or enhanced in six countries: Ghana, Kenya, Mali, Nigeria, Tanzania, and Uganda. One especially promising training program has been established at Uganda, where NIAID and the Foundation for the National

[158] https://grants.nih.gov/grants/guide/pa-files/PAR-18-901.html.
[159] https://www.fic.nih.gov/Programs/Pages/environmental-occupational.aspx.
[160] https://www.genome.gov/27563951/an-international-summit-in-human-genetics-and-genomics/.
[161] https://www.fic.nih.gov/News/Pages/2018-hiv-aids-mentoring-supplements-fellows-scholars.aspx.
[162] https://www.fic.nih.gov/Funding/Pages/collaborations-h3africa.aspx.

Institutes of Health (FNIH) are also supporting the launch of a Center for Excellence in Bioinformatics and Data Intensive Sciences through public–private partnerships.

NIEHS has also launched a new Environmental Health working group for H3Africa in collaboration with the Wellcome Trust. With the H3Africa consortium as a forum to discuss environmental risk factors relevant to the program's studies, a series of educational webinars were presented on topics such as exposure science, including the logistics of sample collection, measures; the basics of environmental epidemiology; and microbiome data from distinct African populations.[163]

NIEHS and NIAID collaborated on training workshops held at the International Conference on One Medicine, One Science, meetings in 2017 and 2018. Trainings have included a new training module for LMICs on the NIH grant application process, application of a One Health paradigm to environmental health research generally and on Zika, Arctic contamination, chronic kidney disease of unknown origin (CKDu), and the BP Oil Spill response. Presentations at the conferences have focused on a broad range of environmental health and infectious disease research enterprises. Federal and academic collaborators include CDC, FDA, the National Oceanic and Atmospheric Administration (NOAA), and the University of Minnesota.[164]

Intramural Activities

The NIH IRP provides opportunities for students, postdoctoral scholars, and clinicians to contribute to research within the more than 1,100 NIH intramural laboratories. The IRP is located on several NIH campuses across the country with investigators aligned to each IC. Principal investigators work with scientific colleagues both nationally and internationally, thus providing a strong research training experience for future investigators, as well as continued professional development of intramural scientists.[165]

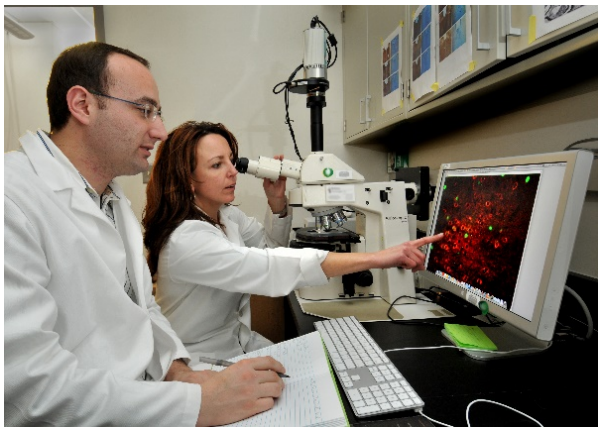

Figure 4. Jennifer Bossert reviewing data imagery in the NIDA IRP Neurobiology of Relapses Section. Unknown photographer.

[163] https://www.niehs.nih.gov/news/events/pastmtg/2018/ehia/index.cfm.
[164] http://comos.umn.edu/icomos.
[165] https://irp.nih.gov/.

Each IC has developed IRP training in line with its mission. For example, the NIDCD Otolaryngology Surgeon-Scientist Program advances NIDCD's programmatic priority to promote biomedical and clinical research training and career development in collaboration with Johns Hopkins University, Georgetown University Medical Center, and Walter Reed National Military Medical Center. This translational and clinical research program complements the rich, basic science research within NIDCD and other Institutes in the NIH intramural program. Areas of priority and opportunity include disorders affecting hearing, balance, taste, smell, voice, speech, and language. Current programs have advanced the capability for preclinical and clinical studies for interventions in these disorders.[166] NLM's IRP training provides opportunities for postdoctoral training and career development, as well as opportunities for high school, college, graduate students, medical professionals, and visiting scientists on sabbatical. In FY 2018, NLM supported 63 fellows in short-term and multiyear training in pursuit of NLM's goal to expand training in biomedical informatics and data science and recruit diverse and highly qualified trainees.[167,168]

After completing a terminal degree, individuals may join the IRP as fellows.[169] Fellowship includes programs for clinicians for whom NIH offers opportunities for residency and subspecialty training and accredited graduate medical education programs. For program completion data, see Appendix E.

The CC provides a robust array of training resources through the Office of Clinical Research Training and Medical Education. These include training opportunities for students, recent graduates, residents, fellows, and practicing clinicians in areas ranging from pharmacy and bioethics to critical care and imaging, among others.[170]

The Rocky Mountain Laboratories–Bethesda Postdoctoral Fellowship Program is a collaborative partnership between NIAID laboratories located in Montana and Maryland. This program fosters scientific exchange and collaboration between NIAID laboratories in different geographic locations while offering a unique postdoctoral training environment. Each fellow has two mentors, one in Montana and one in Maryland, and divides his or her time between the two laboratories while working on a collaborative research project.[171]

Among the IRP's offerings are summer internships for high school, college, and graduate students and year-long engagements for students in graduate or professional school. The Graduate Partnerships Program enables students to pursue research toward their degrees at NIH in partnership with a participating academic institution.[172] The analogous Medical Research Scholars Program provides research-oriented medical, dental, and veterinary students an opportunity to engage in a mentored clinical or translational research project on the NIH campus.[173]

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[166] https://www.nidcd.nih.gov/training/otolaryngology-surgeon-scientist.
[167] https://www.ncbi.nlm.nih.gov/research/postdocs/.
[168] https://lhncbc.nlm.nih.gov/biomedical-informatics-training-program.
[169] https://www.training.nih.gov/programs/postdoc_irp.
[170] https://clinicalcenter.nih.gov/training/index.html.
[171] https://www.niaid.nih.gov/about/rocky-mountain-bethesda.
[172] https://www.training.nih.gov/programs/gpp.
[173] http://www.cc.nih.gov/training/mrsp/index.html.

Figure 5. Members of the NIH Medical Research Scholars Program conduct research in the CC. Credit: CC.

The Deputy Director for Intramural Research Innovation Awards program was launched in 2016 by OIR. To support career development and stimulate innovative, high-impact research and foster collaborations, the program offers intramural investigators three types of awards: a program project award for a team of three to five independent investigators, a center/facility award, and an award for collaborations with extramural investigators or industry. In 2017, scientific fields that were identified as priorities included inflammatory diseases, cell-based therapies, microbiome, drug resistance, neuroscience, RNA biology and therapeutics, vaccines, natural products, and animal modeling, although research in other topics was also considered. The program made 25 awards to intramural investigators, ranging from $48,000 to $750,000 each, with a total of $6.9 million dollars awarded.[174]

Assessments of Career Programs and the Scientific Workforce

The challenge of training and maintaining the biomedical research workforce is complex—it requires engagement with multiple stakeholders, contributors, and partners; attention to all career stages of current and potential trainees; and judicious investment. As such, regular analysis and evaluation is required. A variety of data systems, analytical methodologies, and evaluation techniques are used to keep NIH informed of the current state and to understand the needs of the nation.

Since the NRSA program was established in 1974, NIH training programs have been reviewed and evaluated regularly. In particular, NRSA program processes and outcomes are assessed through recurring program evaluations, and performance is evaluated annually using GPRA measures. OER, which oversees the NRSA program, coordinates these reviews.

Every year, NIH reports on NRSA research training outcomes and program management using two GPRA measures that assess the quality of its programs and determine whether substantial numbers of trainees and fellows are retained in research careers. Specifically, NIH compares the proportion of former NRSA trainees and fellows who apply for and receive NIH research grant support with that of their peers.

[174] https://oir.nih.gov/about/ddir-innovation-awards.

Subsequent NIH support received by these trainees is one of several indicators that reflect the impact of NRSA research training on participants' ability to successfully pursue and sustain a research career. To date, NRSA trainees and fellows have consistently outperformed their counterparts on these measures.

In addition to scheduled NIH-wide assessments of programs coordinated through OER, individual ICs undertake periodic, targeted evaluations to improve implementation and assess outcomes of their own training programs.

For example, the NIEHS Office of Fellows Development created a tool to track the career paths of postdoctoral fellows in the NIEHS IRP and analyze the data to help science administrators better understand the numerous factors that contribute to career decisions of their fellows.[175,176] The method is the first to standardize categories of career outcomes of NIEHS postdoctoral fellows and separates employment trends in biomedical science by sector, type, and job specifics based on detailed career outcomes from more than 900 NIEHS postdoctoral fellows over the past 15 years.

The methods used to monitor and address challenges in the biomedical workforce are also active areas of research. Experts from relevant research disciplines were brought together for a Workshop on Developing a Data Science Competent Environmental Health Science Workforce to examine existing data science and environment, health and science (EHS) resources, such as the trainee pipelines, availability of mentors, and research; identify how these resources can address EHS-specific training goals in data science; and make recommendations for NIEHS, specifically for training within the field of data science.[177]

In recent years, NIGMS also has assessed the career outcomes of trainees in its MARC program and the postdoctoral scholars participating in its Institutional Research and Academic Career Development Awards career development program.[178] Evaluating outcomes of 1986–2013 trainees, the assessment concluded that, despite significant variability in grantee reporting and difficulty in monitoring students' movements over time, about 70 percent of program alumni are enrolled in or have earned a subsequent graduate degree in a health-related discipline.

Available information regarding postdoctoral scholars participating in the Institutional Research and Academic Career Development Awards (IRACDA) career development program indicates that 73 percent of IRACDA alumni are in academic research and/or teaching positions, which is higher than the 43 percent of the overall biomedical workforce going into these positions cited in a 2012 NIH Biomedical Workforce Working Group Report.[179]

Along a similar vein, NLM carried out an analysis of core skills for data scientists to inform training of biomedical data scientists,[180] providing recommendations for a minimal set of core skills for biomedical

[175] https://www.niehs.nih.gov/news/newsroom/releases/2018/january24/index.cfm.
[176] Xu H, et al. *Nat Biotechnol* 2018;36(2):197-202. PMID: 29334368.
[177] https://www.niehs.nih.gov/news/events/pastmtg/2018/data-science/index.cfm.
[178] https://www.nigms.nih.gov/about/council/minutes/Pages/may19-20_2016.aspx.
[179] https://acd.od.nih.gov/documents/reports/Biomedical_research_wgreport.pdf.
[180] Zaringhalam, et al. *Core Skills for Biomedical Data Scientists.*
https://www.nlm.nih.gov/pubs/reports/core_skills_draft_report_v2.pdf.

data scientists based on analysis that draws on opinions of data scientists, curricula for existing biomedical data science programs, and requirements for biomedical data science jobs. The core competencies included general biomedical subject-matter knowledge, programming language expertise, predictive analytics, modeling, machine learning, team science and scientific communication, and responsible data stewardship.

NLM researchers conducted interviews with 13 internship program graduates or participants to evaluate a graduate-level internship for library science students who are interested in serving Latino or Native American populations. The analysis suggests that the program increased participants' interest in health sciences librarianship and led to improved career opportunities, both in health sciences libraries and other libraries with health information programming. It also highlights specific factors that are likely to contribute to the strength of career pipeline programs aiming to bring students who are interested in serving Latino and Native American communities into health librarianship. Exposing graduate-level interns to a broad range of health sciences librarianship tasks, including outreach to Latino and Native American communities and formal mentorship, is likely to maximize interns' interests in both health sciences librarianship and service to these communities.[181]

NLM also carried out a comprehensive longitudinal analysis of data science training at NIH, in both intramural and extramural programs, and identified important needs and opportunities.[182] Five broad recommendations were made to help create a diverse workforce prepared to respond to the challenges and seize the opportunities of an increasingly open and data-intensive biomedical research enterprise. These include (1) developing a common programmatic understanding of what constitutes biomedical data science and its practice (both of which will evolve); (2) expanding and enhancing training of data science experts; (3) providing training across data science, biomedical science, and information science; (4) promoting a data science–literate biomedical workforce; and (5) fostering programmatic coherence for biomedical data science training and workforce development across NIH.

Science Education and Literacy

To remain a world leader in biomedical research, the U.S. must encourage and support students' curiosity and interest in science throughout their education to spark an interest in science in those who may go on to pursue a career in science. In addition, fostering scientific and health literacy in the general public will help to improve the health of the nation, improving the uptake of scientific findings and health information as it is communicated to the public. NIH funds a number of science and research education and literacy activities from elementary school through college. These programs support curriculum development, mentoring, outreach, and research experiences designed to recruit individuals with specific backgrounds to research careers or to enhance the diversity of the biomedical workforce.

[181] Kesselman A, et al. *J Med Libr Assoc* 2016;104(4):328-332. PMID: 27822159.
[182] National Library of Medicine Data Science Coordinating Unit Workforce Excellence Team. *Report to the NLM Director: The State of Data Science Workforce Development.* 2018. https://www.nlm.nih.gov/pubs/reports/state_of_data_science_training_report_final2.pdf.

NIH Activities to Promote Science Education and Literacy

NIH programs to share science with the public start with pre-kindergarten audiences and continue through primary and secondary education into adulthood.

Environmental health literacy is an important and distinct form of health literacy that focuses on addressing the sources of pollution and promoting behavior changes that prevent or mitigate exposure to pollutants. NIEHS has worked to develop recommendations for the most effective ways that researchers can ensure that the translation of research findings will lead to greater understanding of specific risks, reduction of exposures, and improvement of health outcomes for individuals and communities.[183,184]

Science Take-Out Kits, funded through the NIEHS SBIR/STTR program, provide hands-on activities for high school students to learn about important concepts in environmental health science. The kits also improve the public's understanding of how the environment impacts health.[185]

Complementing these efforts, NIEHS' Partnerships for Environmental Public Health developed a series of podcasts that explore how exposures affect the public's health. Each episode highlights ways researchers work in partnership with community groups to understand and address environmental health issues.[186] Examples of podcasts include *Circadian Rhythm and Your Health* and *Crumb Rubber in Playgrounds and Children's Health.*

NCCIH has launched *Know the Science*, an initiative clarifying and explaining scientific topics related to health research. This effort features a variety of materials—including interactive modules, quizzes, and videos—to provide engaging, straightforward content for visitors to dive in and get to know the science covering topics common to all areas of health research.[187]

Designed for and tested by upper-elementary and middle school children, *NEI for Kids* makes learning about vision science and eye health fun. Children visiting the website will find NEI's award-winning *Ask a Scientist* video series, optical illusions, healthy vision tips, an animated video explaining the visual system, and much more.[188]

NEI has also developed a virtual reality application that simulates the experience of living with visual impairment from either cataract or age-related macular degeneration (AMD). The app is accessed through a fully immersive, high-end headset that enables users to experience cataract and age-related macular degeneration in two different scenes: a nighttime cityscape and a grocery store aisle. During use, the app provides short audio descriptions of the eye conditions. A Google Cardboard version for use with iPhone is in under development. The communications office also has developed a promotional video to

[183] Finn S, et al. *Environ Health Perspect* 2017;125(4):495-501. PMID: 26126293.
[184] Editors: Finn S, et al. *Environmental Health Literacy.* Springer, 2019. https://springer.com/la/book/9783319941073.
[185] https://www.sciencetakeout.com.
[186] https://www.niehs.nih.gov/research/supported/translational/peph/podcasts/index.cfm.
[187] https://nccih.nih.gov/news/press/Know-the-science-initiative.
[188] http://www.nei.nih.gov/kids.

summarize a forthcoming clinical trial that uses patient stem cells to treat AMD. Together, these videos demonstrate the profound impact disease can have on vision and what NEI is doing to address it.[189]

NIBIB's *Surgery of the Future* app is an interactive experience that highlights research technologies funded by NIBIB that improve surgical procedures. The app allows users to move through a virtual operating room to learn about such technologies as new imaging tools, robotics, biomaterials, and more.[190]

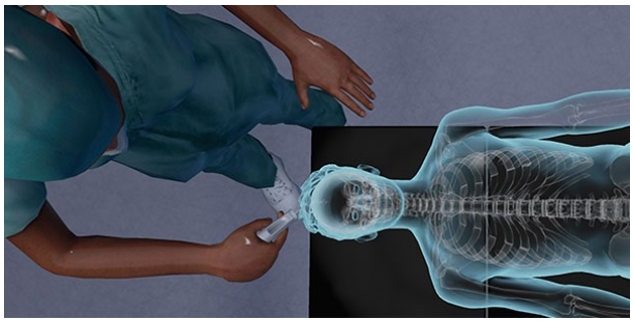

Figure 6. The NIBIB Surgery of the Future app. Credit: NIBIB.

The Science Education Partnership Award (SEPA) program supports education activities for pre-kindergarten to grade 12 students to (1) enhance the diversity of the future biomedical, behavioral, and clinical research workforce and (2) foster a better understanding of NIH-funded biomedical, behavioral, and clinical research and its public health implications.[191] SEPA funded 22 new awards in FY 2016 and 14 in FY 2017, when it was transferred to NIGMS from NIH OD, and 16 in FY 2018. Of the 66 currently active SEPA projects, 15 are based in states that also host Institutional Development Award (IDeA) programs, which—by supporting basic, clinical, and translational research, faculty development, and infrastructure improvements—build research capacities in states that historically have had low levels of NIH funding. The SEPA program also includes a new, innovative SBIR/STTR element entitled Interactive Digital Media STEM Resources for Pre-College and Informal Science Education Audiences.[192] In FY 2018, 14 SEPA SBIR/STTR awards were funded.

NIH also supports formal opportunities for training for educators. In partnership with the North Carolina Association for Biomedical Research, the Science, Teachers, and Research Summer (STaRS) Experience offers a 2-week hands-on professional development workshop for 10 North Carolina high school science teachers each year. The teachers take information, activities, and a lesson plan back to their classrooms.[193]

In addition to promoting scientific literacy, NIH also supports efforts to make scientific information readily available. The 7,100-member institutions of the National Networks of Libraries of Medicine (NNLM) are valued partners in ensuring that health information, including from NLM services, is available to scientists,

[189] https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/see-what-i-see-virtual-reality-eye-disease-experience.
[190] https://www.nibib.nih.gov/Surgery-of-Future.
[191] https://nihsepa.org/.
[192] https://www.sbir.gov/sbirsearch/detail/1317757.
[193] https://www.niehs.nih.gov/research/supported/training/supplements/student/index.cfm.

health professionals, and the public. NNLM has a partnership with the NIH *All of Us* Research Program to support community education and engagement activities designed to raise awareness about the program to library audiences. The partnership also provides a learning platform for and about *All of Us* for the program's entire community, including participants, researchers, program providers, and partners. In FY 2018, NNLM formed the *All of Us* Community Engagement Network, which is the subset of NNLM members who support, promote, and lead *All of Us* engagement activities in libraries. The main goals are to increase capacity for public library staff to provide health information services for their patrons and to blanket the nation with *All of Us* awareness through library activities. As of December 2018, NNLM's partnership with the *All of Us* Research Program has reached 16 states. Additionally, NNLM's *All of Us* Training and Education Center operates the program's learning platform. In FY 2018, the platform was launched with an initial training offering required for new program providers.[194]

Figure 7. NIH Director, Francis Collins, M.D., Ph.D., answers questions during the 2017 National DNA Day Twitter Chat. Credit: Ernesto del Aguila III, NHGRI.

Throughout the year, various ICOs also host and coordinate events promoting particular aspects of health research. For example, every year on April 25, NHGRI and partner organizations—including schools, museums, research institutions, and nonprofits—celebrate National DNA Day by hosting events that give the public an opportunity to learn more about genomics. For National DNA Day 2018, NHGRI launched a special public awareness campaign called the *15 for 15 Celebration* to commemorate the 15th anniversary of the completion of the Human Genome Project.[195,196] The *15 for 15 Celebration* was a social media–driven campaign that ran April 5–25, 2018. During this period, NHGRI unveiled, day by day, a total of 15 ways that genomics has and will continue to transform our society. Overall, 80 registered DNA Day Events took place in 26 states and Washington, D.C., 8 events took place in 5 countries outside the U.S., and 5 state proclamations and 1 senate resolution declared April 25 as DNA Day.

In March 2017, NHGRI and FNIH hosted a meeting titled *Genomic Literacy, Education, and Engagement (GLEE)*. *GLEE* drew almost 160 individuals from academia, industry, community-based organizations,

[194] https://nnlm.gov/allofus.
[195] https://www.genome.gov/10506367/national-dna-day/.
[196] https://www.genome.gov/27570876/15-for-15-celebration/.

nonprofits, government, and K–16 education organizations to discuss how to enhance genomic literacy among three audiences: K–16 students, the general public, and health care providers. *GLEE* is one component of NHGRI's long-standing commitment to genomics education and community engagement.[197]

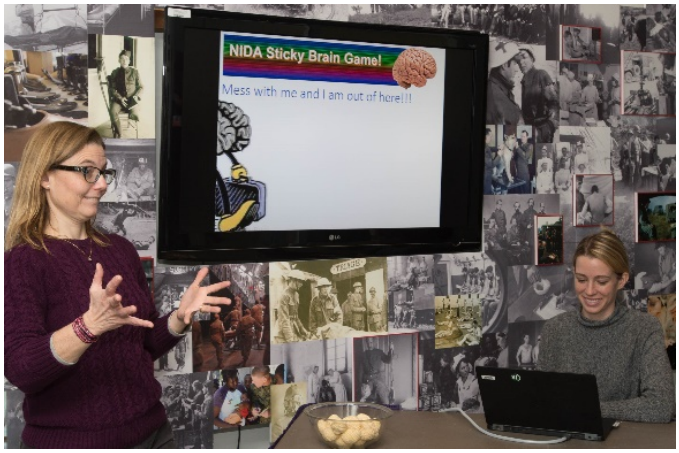

Figure 8. Students enjoying the 19th annual Brain Awareness Week program at the National Museum of Health and Medicine in Silver Spring, Maryland, on Thursday, March 15, 2018. Credit: National Museum of Health and Medicine photo by Matthew Breitbart/Released.

Brain Awareness Week—an annual global public outreach partnership of government agencies, universities, hospitals, patient advocacy groups, scientific societies, service organizations, and schools—is celebrated each March.[198] The purpose of Brain Awareness Week is to increase public awareness of the progress and benefits of brain research. NIMH and NINDS co-lead NIH Brain Awareness Events in collaboration with other NIH Institutes (NCI, NEI, NIA, NIAAA, NICHD NIDA, NIDCD). NIMH participates by hosting school visits, community lectures, and lab tours that introduce the public to the world of neuroscience and its role in advancing the understanding of mental illnesses.[199]

NLM launched a new exhibit entitled *Graphic Medicine: Ill-Conceived and Well Drawn!* which explores the emerging genre of medical literature that combines the art of comics and personal illness narrative. This approach can reveal the emotional power of these narratives and the clinical data they often involve. These stories are an essential way to understand effective treatment, healing, and understanding. Artist, educator, and *New York Times* bestselling author Ellen Forney guest curated the exhibition, which acknowledges and celebrates NLM's newly acquired collection of graphic medicine publications. The accompanying website received the 2018 Communicator Award from the Academy of Interactive and Visual Arts, an assembly of professionals from various disciplines of the visual arts dedicated to embracing progress and the evolving nature of traditional and interactive media.[200]

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[197] https://www.genome.gov/27568594/genomic-literacy-education-and-engagement-glee-initiative/.
[198] http://www.dana.org/baw/.
[199] https://www.niaaa.nih.gov/news-events/news-releases/students-explore-brain-nih-scientists-nih-celebrates-brain-awareness-week.
[200] https://www.nlm.nih.gov/news/graphic_medicine_exhibition_2018.html.

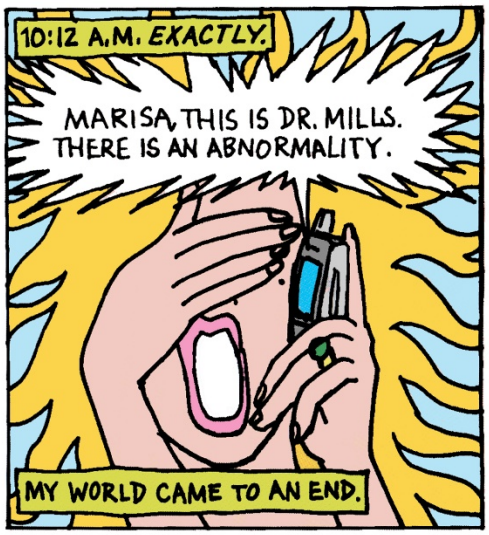

Figure 9. From Cancer Vixen: A True Story, Marisa Acocella Marchetto, 2006. Cancer Vixen is the story of author and artist Marisa Marchetto's diagnosis of breast cancer and her subsequent treatment. In this panel, Marchetto shows us the moment of her diagnosis—when her world as she had known it came to an end. Credit: Marisa Acocella Marchetto and Penguin Random House LLC.

Engaging Different Communities

NIH also works to support science education and literacy outreach to specific communities. In partnership with the other organizations, the National Eye Health Education Program (NEHEP) facilitated in-person workshops on diabetic eye disease for *promotoras*—Hispanic/Latino community members who are not professional health workers—and community health workers that reach Hispanic/Latino communities.[201] The *promotoras* learned about eye health, as well as how to increase awareness among Hispanics/Latinos, especially among people with diabetes. During the workshops, which were conducted in Spanish, participants engaged in interactive exercises to learn about diabetic eye disease and the importance of visiting an eye care professional for a comprehensive dilated eye exam. The participants also practiced using the *Diabetes and Healthy Eyes Toolkit* and explored NEHEP's other educational materials.[202]

[201] https://nei.nih.gov/nehep/programs/ojo.
[202] https://nei.nih.gov/nehep/programs/diabeticeyedisease/toolkit.

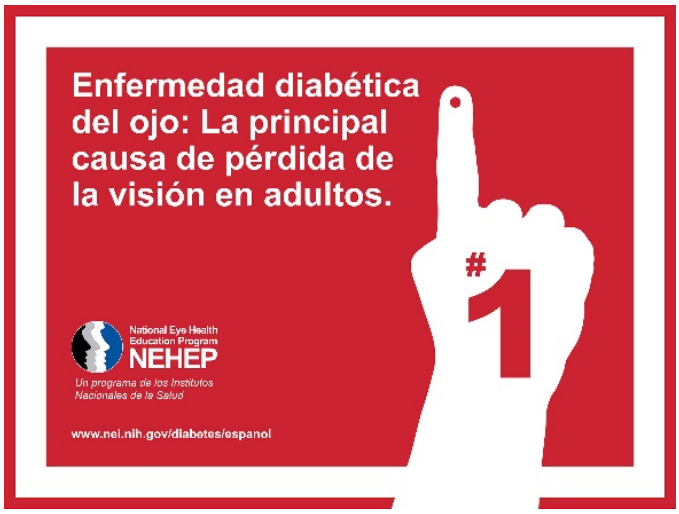

Figure 10. Part of the NEI's Diabetic Eye Disease educational materials, an infocard communicating in Spanish that Diabetic Eye Disease is the number one cause of vision loss in working-age adults. Credit: NEI.

In FY 2016 and 2017, NLM partnered with the South Carolina Area Health Education Centers (AHEC) on several projects to promote teen and adult health information literacy. For example, in one project, students researched public health themes to create educational comic books geared toward middle school students: *Smoking Stinks*, *Double Cup Dilemma*, and *Mind Over Matter*. In the process, the high school students learned about helpful resources available from the NLM; gained valuable communication, research, and creative skills; increased their knowledge about health careers; and improved their health literacy.[203] In another project, NLM and the National AHEC Organization (NAO) collaborated to test a previously developed teen health information literacy model in various contextual situations, such as urban settings and frontier regions. The project aimed to improve health knowledge, health information literacy, interest in health careers, community engagement, and leadership and communication skills of teens in disadvantaged communities.[204]

Hands-On Science Education

For those particularly interested in gaining hands-on experience, NIH also supports programs that empower participants to apply the concepts behind health research. These opportunities range from citizen science projects—defined by the NIH Citizen Science Working Group as "a collaborative approach to research involving the public, not just as subjects of the research or advisors to the research but as direct collaborators and partners in the research process itself"—to more intensive experiences in conducted laboratories under the guidance of current researchers.

NLM is committed to encouraging citizen science as a way to provide opportunities for members of the community to work with NLM to improve and apply NLM products and services in novel ways. In part, NLM accomplishes this through community-based codeathons, which are hands-on, team-based training

[203] https://www.scahec.net/comics/.
[204] Keselman A, et al. *J Med Libr Assoc* 2019;107(1):72-79. PMID: 30598651.

projects that engage community members to work with NLM staff to improve its products and services. In FY 2018, NLM conducted 14 codeathons on such topics as novel virus discovery and reproducible bioinformatics platforms.[205]

The NIEHS AirQuality Treks project is an SBIR/STTR-funded citizen science project that allows students to design and carry out their own air pollution monitoring experiments using handheld air pollution monitors.[206] Data collected by students are uploaded into a database and displayed on an interactive map for the students to analyze and comment on in a blog format.[207]

The Design by Biomedical Undergraduate Teams (DEBUT) Challenge, supported by NIBIB and VentureWell, offers undergraduate bioengineering students an opportunity to develop technologies to address real-world health problems.[208,209] In 2018, the first-place prize of $20,000 went to a team from Johns Hopkins University in Baltimore for a minimally invasive brain retractor, Radiex, that provides safer surgical access to the brain for neurological operations.

Summary

NIH is the nation's medical research agency, driving research that is focused on making important discoveries that improve health and save lives. Overseen by the NIH OD, each of the 27 ICs has its own specific research agenda, often focusing on particular diseases or body systems. This chapter provided an overview of the structure of NIH, including its role in furthering biomedical research and ensuring that training and education in the biomedical sciences are available to people of all ages and stages of career development. Chapter 2 presents an overview of the biomedical research that NIH supports.

[205] https://biohackathons.github.io/.
[206] https://www.aqtreks.com/index.html.
[207] https://aqtreks.airqdb.com/treks/.
[208] https://www.nibib.nih.gov/training-careers/undergraduate-graduate/design-biomedical-undergraduate-teams-debut-challenge.
[209] https://www.nih.gov/news-events/news-releases/assistive-surgical-devices-shine-debut-biomedical-engineering-design-competition.

Chapter 2 Overview of NIH Research

Introduction

In pursuit of its mission, NIH conducts and supports biomedical and behavioral research across a broad spectrum of scientific disciplines and approaches. NIH research focuses on both ongoing and newly emerging public health needs. As these needs are identified, scientific approaches are utilized across a continuum of research designed to understand the basic causes and mechanisms of disease, find new ways of identifying and interrupting disease processes, and bring these new interventions into common practice for the public benefit.

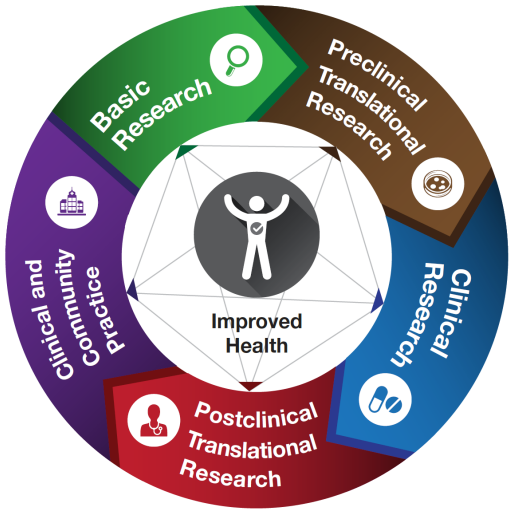

Figure 11. NIH supports the full continuum of biomedical research.

The continuum, from basic research to practice, is summarized below and illustrated in Figure 11. NIH activities that relate to each stage of this continuum are then described in more detail in subsequent sections of this chapter. It should be noted, however, that the path from basic research to clinical and community practice is not a continuum in the strictest sense because all stages of biomedical and behavioral research—from basic to translational to clinical—can inform other areas. For example, findings in clinical research can provide new areas of inquiry in basic science (see feedback arrows in Figure 11).

Basic Research

The research continuum begins with basic research—the study of the fundamental mechanisms of biology and behavior. Investments in basic biomedical and behavioral research make it possible to understand

the causes of disease onset and progression. Basic research is essential to the development of better diagnostics, the design of preventive interventions, and the discovery of new treatments and cures. Thus, basic research is a critical component of the nation's public investment in research and a central feature of the NIH research program.

Preclinical Translational Research

Realizing the benefits of fundamental biomedical discoveries depends on the translation of knowledge into the development of new diagnostics, therapeutics, and preventive measures. NIH is a key supporter of preclinical translational research—studies that serve as a bridge between basic research and human medicine. Early translational investigations are often carried out using animal models, cell cultures, samples of human or animal tissues, or a variety of experimental systems, such as computer-assisted modeling of disease progression and drug therapy.

Clinical Research

Medical advances arise from rigorous testing of new strategies for recognizing and intervening in disease processes, whether intervention occurs before the processes manifest (prevention) or after they take hold (treatment). Clinical research[210] is research that is conducted with human subjects and includes patient-oriented studies, such as clinical trials.[211]

Postclinical Translational Research

For evidence-based research to have an impact on public health, NIH must ensure that new diagnostics and interventions reach the populations that need them most: patients, families, health care providers, and the broader public health community. The postclinical translational stage takes results from studies in humans and investigates the best methods for giving those results broad applicability. NIH supports

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[210] Clinical research is defined by NIH as research with human subjects that falls in one of the following categories:

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that use human tissues that cannot be linked to a living individual. The research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

(2) Epidemiological and behavioral studies.

(3) Outcomes research and health services research.

Studies falling under 45 CFR 46.101(b) (4) (Exemption 4) are not considered clinical research by this definition.
https://grants.nih.gov/grants/glossary.htm#C.

[211] Clinical trials are defined by NIH as follows:
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
See Common Rule definition of research at 45 CFR 46.102(d).
See Common Rule definition of human subject at 45 CFR 46.102(f).
https://grants.nih.gov/grants/glossary.htm#C.

postclinical translational research to identify factors that enhance access to and implementation of new interventions, with the aim of optimizing the health care delivery system to reflect the latest medical advances.[212] Studies in this area include the development and testing of novel models and methods to best implement newly discovered interventions to reach diverse groups and populations (e.g., racial and ethnic groups, rural populations).

Clinical and Community Practice

As an important part of the NIH mission statement, each IC engages in a broad-based effort to ensure that scientific findings are communicated rapidly and clearly to the public. NIH engages in communication efforts focused on the translation and dissemination of basic and clinical research findings, both through web-based initiatives and directly to hospitals, doctors' offices, and community settings. This dissemination represents the final stage of the NIH research continuum and is key to ensuring that patients reap the benefits of NIH-funded research.

Feedback Between Different Stages of the Research Continuum

The course of NIH research is not a true continuum, in that it does not necessarily progress stepwise, nor does it move in only one direction. All areas of biomedical and behavioral research—basic, translational, and clinical—inform and influence other areas. Basic research scientists provide clinicians with new tools for use with patients, and clinical researchers make new observations about the nature and progression of disease that often produce feedback to stimulate new basic investigations. Research on new outreach approaches and the comparative effectiveness of prevention and treatment strategies not only address the feasibility of the strategies themselves but, in turn, inform the development of future interventions.

Driving the Research Continuum

Population-based, epidemiological research is one of the key drivers of the research continuum. Epidemiological studies provide rigorous statistical evidence of the association between disease and human biology, behavior, or environmental circumstances. These studies motivate research to understand the mechanism of disease and develop methods of prevention or intervention. An overview of NIH's focus on epidemiological research is provided later in this chapter. The NIH research continuum also would not be possible without investment in research resources and infrastructure, as well as the development of new technologies, as described at the end of this chapter.

[212] Within HHS, NIH and the Agency for Healthcare Research and Quality (AHRQ) each support health services research.

Basic Research

Driving progress in biomedical and behavioral sciences in a bottom-up manner, basic research is focused on uncovering the fundamental principles of biology and behavior, as well as understanding the basis of health and disease. From the incremental advances in our understanding of a biological process and how it might err in a given disease to the groundbreaking discoveries that revolutionize our approaches for treating or preventing that disease, investments in basic research lay the foundation for clinical discovery and yield inestimable rewards and benefits to public health.

Basic biological research can involve, but is not limited to, studies performed in computer models, in vitro, in animals, or in humans. This kind of research can fall into one of two categories: (1) research focused on understanding systems, processes, phenomena, and behavior, without a direct connection to human health; or (2) research that seeks to understand the basis and mechanisms of human disease.

Basic biomedical research seeks to understand how finely tuned biological and behavioral processes work together in harmony and how these processes can break down and form the basis of disease. For example, at the molecular level, scientists are interested in understanding how biological macromolecules—proteins, nucleic acids, sugars, and lipids—carry out cellular processes. At the cellular level, researchers focus on understanding how cells sense and respond to their environment; at the behavioral level, researchers concentrate on how individual organisms react to and act upon their environment.

Progress in basic research generally does not follow a linear path from test tubes to cell culture to animal models. Instead, it tends to result from collaborative interactions among research groups across multiple disciplines. The discovery of a disease-causing gene may spark research to determine which proteins that gene produces and how they interact with other molecules. Alternatively, the discovery of a previously unknown protein structure may lead to investigations into the protein's function and the genes that regulate its production. At the heart of every clinical discovery is a body of fundamental basic knowledge that inspires a clinical hypothesis and generates the information required to safely and ethically proceed to testing in humans.

NIH supports a comprehensive portfolio of basic research aimed at understanding fundamental life processes, including basic research that is related to a particular disease, as well as research that may be more broadly applicable. Basic research is encompassed in the missions of ICs across NIH, and progress often requires interdisciplinary approaches to develop new technologies, improve methods of data analysis, and provide insight on fundamental disease pathways. In this endeavor, NIH fosters collaborations that span all the traditional and emerging disciplines of the life, physical, engineering, computer, behavioral, and social sciences. Several key NIH basic research fields are outlined below; updates on specific initiatives are presented in Chapter 3.

Model Organisms and Systems

Basic research is concerned with advancing our understanding of human health and disease; however, for reasons both ethical and practical, many fundamental aspects of biology cannot be studied in people. Therefore, scientists often carry out basic research in "model systems" that are easier to work with in precisely defined and controlled settings. NIH supports both the development of a wide range of research models and individual studies using model organisms. Basic research using model systems and organisms has provided the foundation of knowledge about human growth and development, behavior, maintenance of health, and development of disease. Research on bacteria, yeast, insects, worms, fish, rodents, primates, and even plants has shown that the basic operating principles are nearly the same in all living organisms. Therefore, a finding made in fruit flies or mice may shed light on a biological process in humans and lead to new methods for maintaining human health and diagnosing and treating disease.

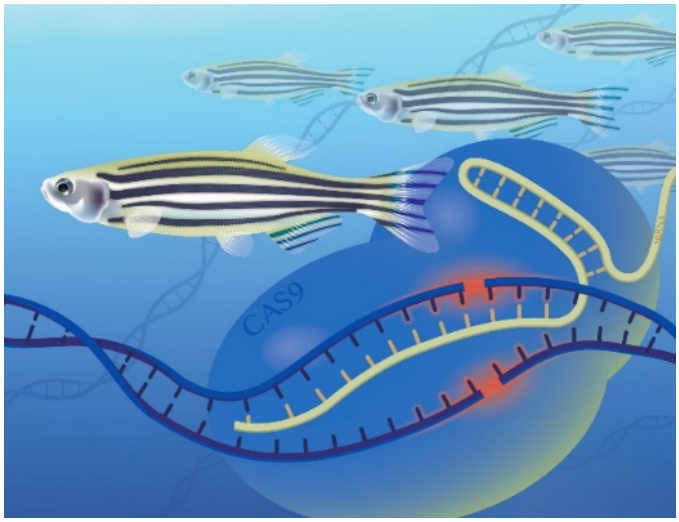

Figure 12. NHGRI scientists are homing in on specific genes in zebrafish to help them better understand the function of genes in people. Credit: Darryl Leja, NHGRI.

When scientists discover that a particular gene is associated with a disease in humans, one of the first steps typically is to find out what that gene does in a model organism. NIH supports the development and distribution of collections of animals with defects in known genes. These animal models can be used to investigate how a particular gene found to be associated with a disease affects development overall, as well as disease susceptibility and progression. For example, the NIH-sponsored National Resource for Zebrafish, Drosophila Stock Center, and Caenorhabditis Genetics Center provide the research community with well-characterized, wild-type (normal) and mutant zebrafish, fruit flies, and roundworms, respectively.

Model organisms often are useful for understanding features of disease that have similar underlying molecular causes. For example, protein-clumping defects are common to several neurodegenerative disorders, such as Alzheimer's, Parkinson's, and Huntington's diseases. Scientists can recreate these cellular defects in yeast, worms, and fruit flies and then translate their findings into knowledge to benefit people with those diseases.

Figure 13. At the largest zebrafish facility in the country, Kevin Bishop, an NHGRI Zebrafish Core staff member, holds up a tank of zebrafish to observe their behavior and physiology. Using molecular techniques, researchers alter the zebrafish's genome to mimic what is seen in human patients in the clinic. Credit: Ernesto del Aguila III, NHGRI.

Cell Biology and Molecular Mechanisms

In the human body, all biological components—from individual genes to entire organs—work together to promote normal development and sustain health. This biological teamwork is made possible by complex molecular machinery that carries out the function of cells and intricate and interconnected pathways that facilitate communication among genes, molecules, and cells.

NIH supports a broad spectrum of research to improve the molecular-level understanding of fundamental biological processes and how to control them. By uncovering how certain molecules function in key signaling pathways, scientists may be able to develop therapies that target these molecules for the treatment of a variety of devastating disorders.

Growth and development is a lifelong process that has many phases and functions. Much of the research in this area focuses on cellular, molecular, and developmental biology to build understanding of the mechanisms and interactions that guide an organism through its development. As for most life processes, when the biochemical choreography of cells goes awry, the result can be disastrous. Glitches in the cell cycle can lead to a host of diseases, most notably cancer, which can be defined simply as uncontrolled cell division and the failure of programmed cell death. Scientists have been taking advantage of the wealth of basic research on the cell cycle to develop anticancer drugs that aim to bolster or block the cell cycle of molecules.

Characterizing Cellular Molecules

-Omics approaches (e.g., genomics, proteomics, metabolomics) characterize such cellular molecules as genes, proteins, metabolites, carbohydrates, and lipids and allow comparisons between species and individuals within a species. Technological advances in -omics have fundamentally changed how molecular biology is studied, making it possible to rapidly obtain information on the entire complement of biomolecules within a cell or tissue. With next-generation sequencing (also known as high-throughput

sequencing), it is now possible to measure the expression of all genes (the transcriptome) in a cell or tissue in less than a day—something that would have taken months, if not years, just a decade ago. Similarly, the speed of sequencing the genome has increased, propelled further by the decrease in sequencing costs over time.

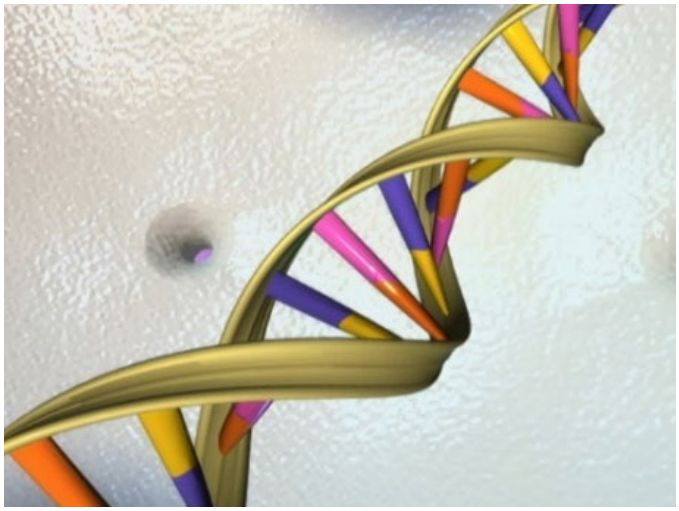

Figure 14. DNA double helix. Credit: NHGRI.

These advances have led to the accumulation of large datasets that scientists sift through using statistical methods, or bioinformatics, to understand how networks of cellular components work in concert to produce a state of normal health and to identify the key players that go awry as a cause or result of disease. For example, scientists may now examine the entire genome of an organism to identify genes associated with a particular trait (e.g., susceptibility to disease, developmental stage, physical traits) or compare the proteome (the entire complement of proteins) of a specific cell type with those of another (e.g., Alzheimer's brain cells versus normal brain cells). The deluge of information has, in turn, generated a pressing need for computerized databases to store, organize, and index the data and for specialized tools to view and analyze the data. NIH's approach to this is discussed under Infrastructure, Research Resources, and Technology Development below.

Genomics

Genomics is the study of an organism's entire genome—the complete assembly of DNA, or in some cases RNA (ribonucleic acid)—that transmits the instructions for developing and operating a living organism. The field of genomics aims to understand how the genetic composition of a cell or an organism contributes to defining development, physiology, and disease. With a map of the human genome now in hand, NIH continues to support research to understand how variations in the genetic sequence among individuals contribute to health and disease.

Genetic analyses—such as genome-wide association studies (GWAS), exome sequencing, and whole-genome sequencing—allow researchers to identify inherited genetic differences, or variants. In turn, these variants may be associated with traits conferring increased risk or protection for specific diseases

and disorders. For example, GWAS compare the entire genome—or the entirety of the genetic material—of individuals with a given trait with that of individuals who do not have that trait.

Figure 15. Timeline of our genomics history. For more information, visit NHGRI's History of Genomics Program.[213] Credit: Ernesto Del Aguila III, NHGRI.

Genomic research focuses not just on individual genes but also on the functioning of the entire genome as a network and, importantly, on how this network interacts with environmental factors to influence health and cause disease. Genomics is a new and challenging discipline that is increasingly used in virtually every field of biological and medical research. To help the public understand genomics, educational resources, including multimedia presentations, are available on the NIH website.[214]

Almost every human disease or disorder has a genetic component and an environmental component. The genetic components of some heritable diseases, such as sickle cell disease or cystic fibrosis, result from mutations in single genes—changes that disrupt the function of the protein they encode. Many health conditions, including common conditions such as heart disease and diabetes, are influenced by many genes in combination with environmental factors. However, in most diseases, the role of genes and the environment is more complicated. Some diseases arise as a result of spontaneous gene mutations that occur during a person's lifetime; others are caused by complex cascades of changes in gene expression triggered, perhaps, by environmental factors. DNA is composed of four chemical building blocks (bases), with the biological information encoded within DNA determined by the order of those bases. Differences as small as one base in our 3 billion pairs of DNA bases can cause disease directly or can cause a person to respond differently to particular pathogens or drugs. Multiple genetic and environmental factors play a role in myriad common diseases and disorders. Not all the genetic risk factors are fully understood, but NIH researchers have begun to identify individual genes or regions of DNA associated with particular conditions. Because of the overwhelming influence of the genome on human health, virtually every NIH IC now engages in genome-related research.

[213] https://www.genome.gov/leadership-initiatives/History-of-Genomics-Program.
[214] http://www.genome.gov/10000002.

Epigenomics

Although an organism's genetic composition is an important determinant of health and disease, additional mechanisms are involved in interpreting the genome and guiding molecular, cellular, and developmental processes. These mechanisms are investigated in the fields of epigenetics, which involves the study of a single gene or sets of genes, and epigenomics, which focuses on more global analyses of epigenetic changes across the entire genome. In the field of epigenetics, scientists are uncovering a complex code of chemical markers that influence whether genes are active or silent, independent of the DNA sequence. Epigenetic processes control normal growth and development and are disrupted in diseases like cancer. Furthermore, such factors as diet and exposure to environmental chemicals throughout all stages of human development can cause epigenetic changes that may turn certain genes on or off. Research in animal models has revealed that even particular parenting behaviors trigger epigenetic changes and alterations in the physiological and behavioral functioning of offspring. Changes in genes that would normally protect against a disease could make people more susceptible to developing that disease later in life. Researchers also believe some epigenetic changes can be passed on from generation to generation.

Epigenomics research is conducted across the ICs and OD. For example, the NIH Common Fund's Epigenomics Program, which ran from 2008 to 2017, developed resources, tools, and technologies to enable investigating the role of epigenomic modifications in human health and disease.[215] Over the course of its duration, the program issued 77 awards and produced 111 reference maps of epigenomic modifications in a variety of healthy human cells and tissues, as well as other resources and tools that are extensively used by the biomedical research community.

Translating the Genetic Code: Transcriptomics, Proteomics, and Metabolomics

Beyond understanding genes and their regulation, NIH also supports investigators in the fields of transcriptomics, proteomics, and metabolomics. Transcriptomics research involves systemwide studies to understand which genes are actually turned on and off and when. Because genes code for the proteins that carry out almost all cellular functions, proteomics focuses on understanding which genes are active and, by extension, the catalog of proteins carrying out cellular functions in a given cell type under particular sets of conditions. This knowledge provides a picture of the molecular players involved in health and disease. In addition to understanding the collective composition of proteins in a cell, researchers also aim to characterize the proteins' three-dimensional structures. Finally, in the field of metabolomics, researchers are using high-throughput methodologies to characterize the types and amounts of metabolic compounds present in our cells and to map the metabolic pathways and networks through which those compounds are generated and regulated.

[215] http://commonfund.nih.gov/epigenomics/index.

Glycomics

NIH also is mapping out additional molecular compounds associated with cellular function. In glycomics, NIH seeks to understand the role of glycans—complex chains of sugar molecules—in various cellular functions. Glycans, which are often found attached to the surface of cells and to proteins on the cell surface, serve important roles in inflammation, heart disease, immune defects, neural development, and cancer. To advance the field of glycomics, NIH supports programs that develop technologies for the analysis of glycans in complex biological systems and has established the Consortium for Functional Glycomics,[216] which provides access to a technological infrastructure for glycobiology in support of basic research. Recent findings indicate that basic research on glycosylation may lead to the development of broad-spectrum antivirals, which could help a person fight off a range of viral infections.

Systems Biology

With the increasing application of -omics and high-throughput technologies, scientists are generating massive amounts of data that can be mined for clues about fundamental life processes, susceptibility to disease, and disease outcomes. To put all this information together across multiple scales, NIH researchers are pioneering the emerging field of systems biology, which draws on biology, mathematics, engineering, and the physical sciences to integrate experimental data with computational approaches that generate models to describe complex biological systems. In addition to describing the interactions among genes, proteins, and metabolites, the models are intended to predict physiological behavior in response to natural and artificial perturbations. By monitoring the effects of a perturbation in virtual experiments, scientists can generate hypotheses that are tested in cellular systems or model organisms to gain a better understanding of the molecular contributions to normal health and disease.

Environmental Factors That Influence Human Health and Disease

NIH supports basic research to understand how environmental factors influence the development and progression of human diseases. The environment includes all physical, chemical, and biological factors external to the person, as well as substances—such as food, water, and air—consumed to support life and health. The more we know about environmental exposures and how they influence various health outcomes, the greater our ability to create healthy environments and to improve our well-being by reducing or preventing hazardous exposures.

NIEHS is dedicated to environmental health research, but other ICs support additional relevant programs and activities. The research topics include air pollution, climate, water quality and sanitation, toxic substances, gene–environment interactions, and other environmental exposures that affect human health throughout the lifespan.

[216] http://www.functionalglycomics.org/static/consortium/consortium.shtml.

Basic Behavioral and Social Science Research

Scientists estimate that human behavior accounts for almost 40 percent of the risk associated with preventable premature deaths in the U.S., rising to 55 percent if societal factors are taken into consideration.[217] Health-injuring behaviors—such as smoking, drinking, drug abuse, inactivity, and poor diet—contribute to many common diseases and adverse health conditions. Furthermore, a convincing body of work, including several NIA-supported studies, indicates that low socioeconomic status, especially low educational attainment, is associated with premature death and more disability, even after considering poor health behaviors.[218,219]

Recognizing the importance of behavioral and social factors in health and disease, NIH supports a broad portfolio of research in the basic behavioral and social sciences. Research in these areas provides fundamental knowledge and informs approaches that are essential for understanding individual and collective systems of behavior and psychosocial functioning; for predicting, preventing, and controlling illness; for developing more personalized (tailored) interventions; for enhancing adherence to treatment and minimizing the collateral impact of disease; and for promoting optimal health and well-being across the lifespan and over generations.

Basic behavioral and social sciences research supported by NIH includes work on behavioral and social processes, biopsychosocial research, and research on methodology and measurement. Within the study of behavioral and social processes is research on behavior change, including the study of factors (e.g., cognitive, social, economic, environmental, developmental) that shape health decision making and the conditions under which knowledge leads to action versus inaction. Meanwhile, basic behavioral economic and decision research approaches are yielding findings that may be translated into effective interventions to change behavior and improve health. In addition, basic research on social networks is improving our understanding of how smoking and obesity spread through socially connected individuals and is providing insight into how these networks might be used to transmit healthy behaviors.

Biopsychosocial research looks at the interaction among biological, psychological, and social processes and includes research on gene–environment interactions and other biobehavioral processes. Examples of basic research in this area examine the processes by which the social environment—and perceived social isolation—affects physiologic processes, including gene expression.

Methodological development in the behavioral and social sciences includes a new emphasis on systems-science approaches. Much like the systems approaches to the biology described above, systems science examines the multilevel, complex interrelationships among the many determinants of health—biological, behavioral, and social—to provide a way to address complex problems within the framework of the "big picture." Systems science involves developing computational models to examine the dynamic interrelationships of variables at multiple levels of analysis (e.g., from cells to society) simultaneously

[217] Schroeder SA. *N Engl J Med* 2007;357(12):1221–8. PMID: 17881753.
[218] Avendano M, et al. *Am J Public Health* 2009;99(3):540-8. PMID: 19150903.
[219] Chapman BP, et al. *Am J Epidemiol* 2010;171(1):83-92. PMID: 19965888.

(often through causal feedback processes), while also studying their impact on the behavior of the system as a whole over time.

Preclinical Translational Research

Translating basic discoveries into new or more effective diagnostics and therapeutics is essential for tackling unmet biomedical needs and improving human health. However, the translational process can be complex, costly, and risk-laden, as evidenced by the fact that less than 1 percent of compounds initially tested actually make it into medicine cabinets. The development of medical devices, imaging techniques, and behavioral interventions follows a similar path. It can take more than a decade before a basic scientific finding is able to advance through preclinical and clinical studies to result in a new treatment, medical device, or prevention method. Furthermore, many promising leads from basic research fail to become proven strategies to address health, often failing in the preclinical stage.

However, advances in biomedical research and technologies have created unprecedented opportunities to transform the translational development pipeline, especially in the preclinical stage. Recent discoveries in basic science have uncovered the molecular mechanisms underlying hundreds of diseases, resulting in many more potential strategies for intervening against disease progression. In addition, high-throughput technologies are more readily available to academic investigators and allow biomedical researchers to pursue these strategies at what would have been an unimaginable pace just a few years ago. For example, high-throughput technology can help identify new therapeutic candidates rapidly, leading to a rigorous optimization process that involves rapid synthesis of chemical variants and the high-throughput screening for effectiveness, selectivity, and toxicity. Furthermore, scientific collaborations are changing the research landscape significantly by enabling projects that no single laboratory could accomplish independently.

NIH is singularly poised to capitalize on these developments. Numerous NIH programs and resources are dedicated to supporting research that moves basic research through to preclinical testing and beyond. NIH also has a unique capability to foster critical multidisciplinary collaborations whose synergistic efforts can lead to new technologies and devices for diagnosing, preventing, and curing diseases and for bringing new discoveries into common medical practice. Similarly, NIH supports the development of consortia, cooperative study groups, and networks that enable a single institution or researcher to combine knowledge and resources with others.

In its unique position, NIH can bring together resources that offer unprecedented opportunities. For example, NIH's ability to create consortia is particularly useful for studying rare diseases because consortia make it possible to recruit sufficient numbers of participants to provide the sample size necessary for preclinical and clinical studies.

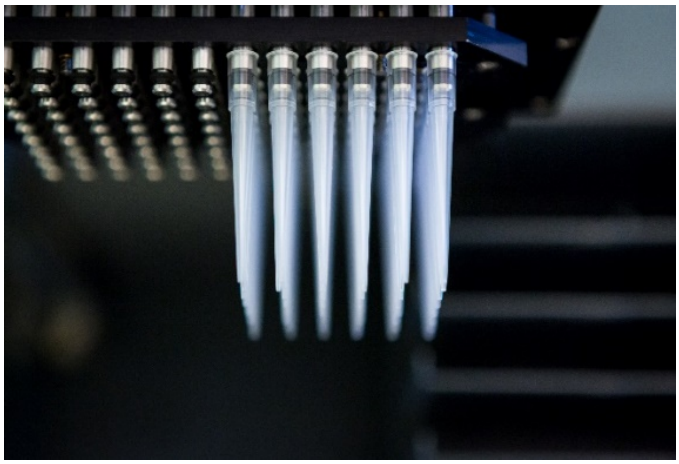

Figure 16. Automated sample handling equipment used in high-throughput in vitro absorption, distribution, metabolism, and excretion assays at NCATS' Drug Metabolism and Pharmacokinetics laboratory. Credit: Daniel Soñé Photography.

This is an exciting time for the advancement of translational science and the speed of development of new cures. Through the application of genomic research, high-throughput technologies, and other advances in basic science, breakthroughs in understanding the causes of many diseases and identifying new targets and pathways for the development of novel therapeutics are within reach. Coupled with these advances, progress in technology and other fields of biomedical research has advanced the potential for the development of new diagnostics and treatments for a wide range of diseases, opening a door of opportunity in translational science, as illustrated in the specific updates throughout Chapter 3.

Clinical Research

Clinical research is the primary source of insight about new means for reducing the burden of illness and improving public health. Clinical research is conducted with human subjects and includes patient-oriented research, such as clinical trials, as well as behavioral and observational studies and outcomes research.

NIH supports many types of clinical trials, which are a crucial subset of clinical research designed to answer specific research questions about biomedical or behavioral interventions. Clinical trials are the best method of determining whether interventions are safe and effective in humans and assessing side effects or other complications. Treatment trials may test experimental drugs, biologics, or devices; new combinations of drugs or biologics; innovative approaches to surgery or radiation therapy; use of new biological therapies, such as gene therapy; or behavioral interventions, such as exercise training or medication adherence. Prevention trials look for better ways either to prevent a disease or to keep it from returning, and they may incorporate research approaches that assess medicines, vaccines, and lifestyle changes, among other interventions. Screening and diagnostic studies are used to find better ways to detect or diagnose diseases or conditions, and quality-of-life trials (or supportive care trials) explore ways to improve people's comfort and ability to continue their activities of daily life, even as they manage chronic illnesses or approach the end of life.

The federal government plays a critical role by supporting important areas of clinical research that are unlikely or rarely addressed by other sectors (e.g., pharmaceutical companies, nonprofit organizations). Specifically, NIH supports clinical and translational studies unlikely to garner substantial investment from other sources because they lack sufficient financial incentives, including studies that address rare diseases, are considered high risk, or are based on lifestyle alterations or behavioral changes, rather than drugs or devices. NIH ICs oversee a broad portfolio of clinical research that encompasses both intramural and extramural programs.

Clinical Resources and Programs

The NIH NCATS CTSA program's goal is to catalyze the translation of biomedical discoveries into better health by creating an integrated research and training environment for clinical and translational sciences and by supporting research resources that local and national research communities need to improve quality and efficiency across the translational research continuum. The NCATS CTSA program seeks to develop a clinical and translational workforce with the skills and knowledge necessary to advance the translation of discoveries, promote collaboration and engagement across a broad range of investigators and stakeholders, integrate translational research within complex populations and across the lifespan, and improve research methods and processes.

NIH Clinical Center

As mentioned in Chapter 1, the CC is conducting approximately 1,600 studies at any given time. Over the years, the CC and its active partners and research participants have contributed to milestone achievements, such as the development of chemotherapy for cancer; the first use of an immunotoxin to treat a malignancy (hairy cell leukemia); identification of the genes that cause kidney cancer, leading to the development of six new, targeted treatments for advanced kidney cancer; demonstration that lithium helps depression; the first gene therapy; the first treatment of AIDS (with the antiretroviral drug azidothymidine); and the development of tests to detect HIV/AIDS and hepatitis viruses in blood, which led to a safer blood supply.

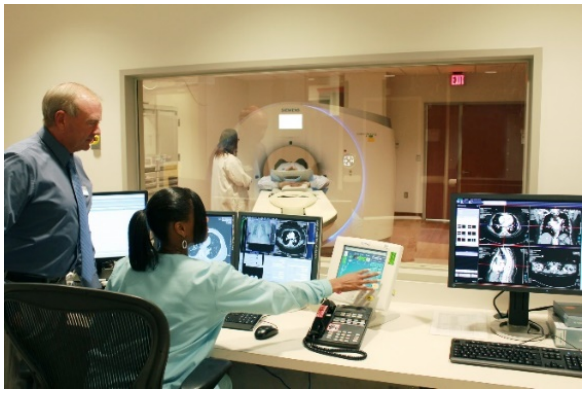

Figure 17. CT scans are an important tool in patient diagnosis and treatment. Since 2014, this CT scanner in the NIH Clinical Center has provided patients and researchers with better quality scans, faster run times, and a lower radiation dose. Credit: NIH.

Investigators outside the NIH campus can access the CC's research resources through a program fostering collaboration with the NIH IRP on projects related to the translation of basic biological discoveries into clinical applications that improve health. This program provides access for external researchers to the CC and, thus, leverages the diverse CC resources, expertise, and infrastructure available to support studies that may not be readily supported elsewhere.[220]

Institute and Center Clinical Research Activities

Nearly all of the NIH ICs support a combination of resources, programs, and initiatives targeted toward strengthening and expanding clinical research. Clinical testing of novel therapies for disorders is critically important to the development of new treatments for patients and is necessary for advancing new research discoveries into clinical practice. However, clinical trials require a significant amount of administrative, financial, and scientific resources, particularly during the startup period when the infrastructure must be established and protocols approved.

ClinicalTrials.gov

The *Food and Drug Administration Modernization Act of 1997 (FDAMA)* required the establishment of a public information resource containing information about federally and privately funded clinical trials testing the effectiveness of investigational new drugs regulated by FDA for patients with serious or life-threatening conditions. The responsibility for building and maintaining the resource was assigned to NIH. Launched in 2000, the *ClinicalTrials.gov*[221] database is managed by the NLM.

The *FDA Amendments Act of 2007 (FDAAA)* expanded the scope and purpose of *ClinicalTrials.gov*, requiring more types of clinical trials to be registered in *ClinicalTrials.gov* and additional information about those trials to be submitted to *ClinicalTrials.gov*. Specifically, *FDAAA* requires the registration of "applicable clinical trials"—which are, generally, trials of FDA-regulated drugs (other than Phase I), biological products, certain devices, and certain pediatric postmarket surveillance studies of a device—no later than 21 days after enrollment of the first subject. The law also requires the submission of summary trial results, including adverse-event information, generally no later than 12 months after trial completion date. The law includes penalties for noncompliance. As required by the law, the expanded registration database was launched 3 months after the law was enacted; the results database, a year after the law was enacted (September 2008); and the adverse event module, the following year (September 2009).

The *Final Rule for Clinical Trials Registration and Results Information* (42 CFR Part 11) was issued by HHS in September 2016 to clarify and expand the legal requirements for submitting clinical trial information to *ClinicalTrials.gov*, in accordance with *FDAAA*. In particular, the regulations clarify which trials must be submitted and when they must be submitted and expand *FDAAA* by requiring the submission of results information for trials of unapproved products. These regulations became effective in January 2017.[222]

[220] https://clinicalcenter.nih.gov/translational-research-resources/index.html.
[221] https://clinicaltrials.gov/.
[222] https://clinicaltrials.gov/ct2/about-site/history#FinalRuleFDAAA801.

Simultaneously, NIH issued its Policy on the Dissemination of NIH-Funded Clinical Trial Information in September 2016 to promote broad and responsible dissemination of information from NIH-funded clinical trials through *ClinicalTrials.gov*.[223]

Section 2053 of the *21st Century Cures Act* (P.L. 114-255), which was enacted in December 2016, requires submission to *ClinicalTrials.gov* of summary results with valid analyses by sex and gender, as well as race and ethnicity, for NIH-defined Phase III applicable clinical trials. Since December 2017, *ClinicalTrials.gov* has accepted information that indicates plans for conducting valid analyses for each primary outcome measure as part of trial registration information and pre-specified analyses by sex and gender, and race and ethnicity as part of the information on summary results. Section 2054 of the *21st Century Cures Act* required NIH to obtain recommendations on enhancing *ClinicalTrials.gov* by consulting various stakeholders, including patients, researchers, physicians, industry representatives, developers of health information technology, and other federal agencies.[224] In 2017, NLM worked with 18F, a GSA digital services consultancy that conducted research with end users representing various *ClinicalTrials.gov* stakeholders; characterized gaps between the information, search capabilities, and features offered by *ClinicalTrials.gov*, as well as what users expect it to offer; and provided user-oriented recommendations and solutions. *ClinicalTrials.gov* incorporated a series of updates and new features after further development, testing, and validation of the recommendations. These activities are being expanded through a multiyear effort to modernize *ClinicalTrials.gov* to deliver an improved user experience on an updated platform that will accommodate growth and enhance efficiency.

ClinicalTrials.gov is the largest, most frequently used public clinical trial registry and results database in the world. It provides patients, family members, health care professionals, clinical researchers, and other members of the public access to information about clinical trials on a wide range of diseases and conditions. The registry enables users to (1) search for clinical trials of drugs, biologics, devices, and other interventions (by condition, intervention, or sponsor) and obtain information about the studies (e.g., purpose, design, facility locations); (2) track the progress of a study from initiation to completion; and (3) obtain a summary of research results, whether or not they are published. The unique identifier assigned by *ClinicalTrials.gov* to each registered trial has become a de facto standard for identifying clinical trials and is widely and routinely used in medical journal articles, PubMed/Medline citations, Congressional documents, and press releases.

Participation in Clinical Trials

Physicians play a pivotal role in informing, recruiting, and enrolling participants in clinical research trials. Although volunteers in clinical research are more important than ever before, most Americans have never participated in clinical research. Several factors contribute to this lack of participation, including the following:

- Many doctors do not suggest clinical research studies to their patients.

[223] https://clinicaltrials.gov/ct2/about-site/history#FinalNIHPolicy.
[224] https://www.nlm.nih.gov/pubs/techbull/mj17/mj17_clinicaltrials_improve_usability.html.

- Some individuals may not realize the number of possible ways they can contribute to research other than as a patient (e.g., as healthy subjects or taking a survey online).
- Potential participants may not realize they can volunteer directly to be participants in clinical research.
- Stigma may affect recruitment in some studies (e.g., studies of infectious diseases or mental health conditions).
- Many people do not fully understand what a research study is or how studies are carried out. Others may not trust a study's designers or how the study will be conducted. Potential participants may not be convinced of the confidentiality of individual patient data.
- Surveys have shown that most American adults have difficulty using everyday health information to make good health decisions. Information about a trial may be too technical to be easily understood, and forms—such as consent documents—may be too complicated for some individuals to understand and complete.
- Individuals may face any number of logistical challenges, such as transportation, childcare, or time constraints from work.

To address these issues, NIH IC communicators, under the direction of the NIH OCPL, are working to raise awareness among the general public and the medical community of (1) the importance of NIH-supported clinical research to public health; (2) the pressing need for clinical trial participants; and (3) the benefits of clinical trial participation for public health.

To broaden participation in biomedical research, NIH developed an important educational site called *NIH Clinical Research Trials and You*[225] to help people learn more about clinical trials, why clinical trials matter, and how to participate. The resource features information about participating in clinical trials, as well as firsthand experiences from actual clinical trial volunteers and explanations from researchers. The website includes links for locating or enrolling in programs; people can look for trials posted on the *ClinicalTrials.gov* website, as well as trial registries maintained by NIH ICs. Health care professionals can read about evidence-based strategies for talking with patients about trials, print audience-tested posters to help promote trials in their own practices, and find other clinical trial educational materials. OCPL also has developed an equivalent Spanish-language site—*Investigación Clinica*[226]—designed to introduce Spanish-speaking individuals to NIH clinical research and promote NIH compliance with federal language access requirements.

Collaborations and partnerships with communities and stakeholders involved in or affected by NIH research are valuable to all involved, so the *NIH Clinical Research Trials and You* website seeks to develop partnerships with NIH grantees and other stakeholders to assist with a comprehensive awareness-building initiative. To ensure that physicians are aware of their key role in clinical trial recruitment, NIH communications offices are working to increase coordination with their external partners, taking advantage of social media tools to raise physician awareness about clinical research.

[225] https://www.nih.gov/health-information/nih-clinical-research-trials-you.
[226] https://salud.nih.gov/investigacion-clinica/.

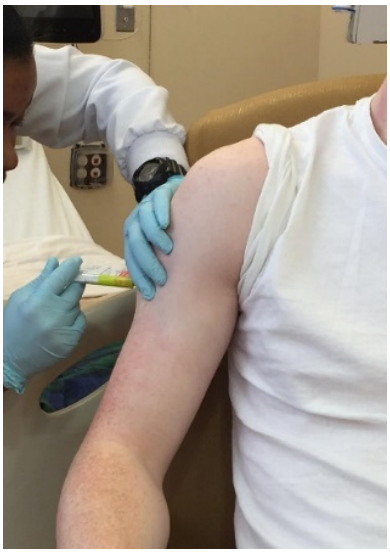

Figure 18. A participant receives an injection in an NIH trial examining a vaccine intended to provide broad protection against a range of mosquito-borne diseases. Credit: NIAID.

Inclusion of Women and Minorities in Clinical Research

The *"*efficacy–effectiveness gap" refers to interventions that show benefit in clinical trials but do not always perform as well in the population at large. One way of reducing the gap involves taking steps to ensure that the scientifically appropriate inclusion of research participants in a given study is representative of the population likely to use the product if it is approved. The *NIH Revitalization Act of 1993* (Public Law 103-43) requires that all NIH-funded clinical research include women and members of minority groups when appropriate to the participants and the proposed research. To meet these statutory requirements, all NIH-funded clinical research is subject to the *NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*.[227]

In accordance with this policy, funding applicants are required to describe what populations will be included in a proposed study, justify any exclusion of specific groups, and provide planned enrollment information. Scientific review groups assess proposed clinical research studies for the inclusion (or exclusion) of individuals on the basis of sex, gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine whether it is justified in terms of the scientific goals and research strategy proposed. Investigators also must report annually their cumulative enrollment data by sex, gender, race, and ethnicity of participants. Inclusion enrollment data are reported in aggregate in *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical* Research (see Appendix F).[228]

[227] http://grants.nih.gov/grants/funding/women_min/women_min.htm.
[228] https://report.nih.gov/recovery/inclusion_research.aspx.

Postclinical Translational Research

Postclinical translational research investigates methods for ensuring that evidence-based interventions are broadly applied and accessible to those who need them the most. HHS pursues this effort primarily through its support of health services research. Health services research is a multidisciplinary field, both basic and applied, that examines how social factors, organizational structures and processes, health technologies, and personal beliefs and behaviors affect access to and use of health care, the quality and cost of health care, and—ultimately—our health and well-being. The goal of health services research is to identify the most effective ways to organize, manage, and deliver high-quality care.[229] Within HHS, AHRQ has primary responsibility for health services research. NIH also plays a significant role in supporting health services research across the government by focusing on questions specific to the missions of each IC. In general, NIH funds health services research in which health outcomes and health-related behaviors are the primary focus and the connection between the subject(s) of the study and improved understanding of health are explicit.

NIH undertakes a number of activities to ensure that the robust evidence base created through basic and clinical research is translated and used to enhance health and reduce illness and disability, as illustrated in specific updates in Chapter 3. The focus of health services research is on optimizing the health care delivery system to supply care based on scientific evidence. As efficacious interventions are developed and tested, a more detailed understanding is needed to establish that they are effective in real-world settings, including ensuring that they are adopted and implemented appropriately and with sustained investment. NIH is especially interested in research designed to understand how innovations in treatment, diagnosis, prevention, and implementation strategies can be deployed most effectively to improve health and well-being, as well as research aimed at designing better interventions with these insights.

Partnering with Health Care Delivery Organizations

Health care delivery organizations are key partners in NIH efforts to study the methods and models for adopting and sustaining evidence-based interventions. Through research within actual health care delivery settings, studies may provide crucial information that can help deliver interventions faster and more effectively. An additional benefit of such partnerships is having access to the immense resources that health care delivery organizations offer, such as electronic medical records for thousands of patients. A number of NIH Institutes already support collaborative activities between health care delivery organizations, such as health maintenance organizations, and biomedical researchers to implement large studies with real-world benefits.

Disseminating and Implementing Clinical Research Discoveries

Dissemination and implementation research is intended to bridge the gap between clinical research and everyday practice by building a knowledge base that addresses how health information, interventions,

[229] https://www.drugabuse.gov/sites/default/files/files/HSRReport.pdf.

and new clinical practices are transmitted and translated for public health and health care service use in specific settings.

Furthermore, NIH partners with other federal agencies to ensure that the evidence produced at NIH is understood and used to its full potential. For example, NIH works closely with AHRQ to create comprehensive, systematic reviews of clinical trials that summarize the state of medical evidence for health care providers and existing gaps for the research community.

Clinical and Community Practice

NIH nurtures strategies that bring basic research discoveries and clinical research findings into practice, with the ultimate goal of improving health outcomes. NIH communication efforts focused on the translation and dissemination of this information to hospitals, doctors' offices, and community settings are key to ensuring patients reap the benefits of NIH-funded research.

It is essential that NIH's communications efforts maintain relevance and credibility with key audiences amid rapidly changing expectations and media formats. Communications products are designed to reach audiences who are more affected by a specific health risk, disease, or disorder; this may be particularly important for medically underserved communities. Through their public information materials, campaigns, and clearinghouses, NIH communications offices continue to respond to changes in health and science communications, including how audiences obtain health and science information.

Disseminating Health Information

NIH has a long history of translating scientific findings into useful information for the public, physicians, nurses, caregivers, and others. NIH partnerships and communication strategies are designed to accomplish this economically and effectively. Health information developed by NIH is based on peer-reviewed, cutting-edge science and is designed to meet the needs of the community and to be easily accessible and understood.

For example, the *NIH MedlinePlus* magazine and its bilingual Spanish counterpart, *NIH Medline Plus Salud*, are quarterly consumer magazines that bring the latest clinical findings to patients and their families. The magazines complement the *MedlinePlus*[230] and *MedlinePlus en español*[231] websites, provided by NLM, that offer trusted, consumer-oriented health information on more than 975 health topics.

An associated resource, MedlinePlus Connect,[232] helps patients and health care providers access consumer health information through a health IT system at the point of need. Patient portals, patient health record (PHR) systems, and electronic health record (EHR) systems can incorporate MedlinePlus

[230] http://www.nlm.nih.gov/medlineplus/.
[231] http://www.nlm.nih.gov/medlineplus/spanish/medlineplus.html.
[232] https://www.nlm.nih.gov/medlineplus/connect/overview.html.

Connect to provide health information for patients, families, and health care providers using standard clinical vocabularies for diagnoses (problem codes), medications, and laboratory tests.

A monthly newsletter by OCPL, *NIH News in Health,*[233] offers the public practical, clear, and to-the-point health news and tips based on the latest NIH research. *Health Information Portal*[234] guides people to relevant, timely health resources from across the NIH website. Both resources bring the most recent and vetted health information to the public in an accessible, user-friendly format. OCPL also produces *Research Matters*,[235] which highlights research accomplishments by NIH and NIH-funded scientists in a blog-like format that seeks to improve public understanding of current science. In 2015, OCPL launched a Spanish-language health information website, *Portal de Información de Salud de NIH.*[236] The webpage offers evidence-based health information from across NIH, on topics ranging from child health to aging. The mobile-friendly site includes translations of many health articles from *NIH News in Health*.

NIH continues to broaden its social media presence more generally, using popular and current outlets through a variety of feeds, subscriptions, and other channels—many of them highlighting the latest priorities and vision of the NIH Director. The NIH Director's blog[237] continues to enhance and broaden the agency's national and international profile. The blog builds on existing agency awareness and education efforts that focus on the public's participation in NIH-funded research and the public's understanding of the value of—and return on—government-funded medical research. The widely read blog, which features news and images from cutting-edge science, as well as opportunities for public feedback, reflects the importance NIH places on communicating biomedical research and telling the NIH story through all forms of media.

Simply communicating scientific breakthroughs and the availability of new treatments does not assure that they will be adopted in common medical practice, nor does simply communicating research results ensure that these results will be used to inform policymaking. In addition to its communication efforts, NIH works with many partners to bring the rich evidence base of NIH research into clinical and community practice, in terms of both treatment and prevention, and into policymaking efforts affecting public health. These partnerships include those engaged in improving health and reducing the burdens of disease within HHS (e.g., FDA, CDC, AHRQ) and across the U.S. government, such as the VA and the U.S. Department of Defense (DoD). NIH also partners with nongovernmental agencies, scientific organizations, patient advocacy groups, and health care delivery systems. These partnerships provide the American public with a health care system that will enhance health, lengthen life, and reduce illness and disability.

Targeted Health Communication Programs

Millions of Americans search online daily for answers to health-related questions, and they look to NIH for authoritative, reliable, research-based health information. NIH communicators at the agency's 27 ICs

[233] https://newsinhealth.nih.gov/home.
[234] https://www.nih.gov/health-information.
[235] https://www.nih.gov/news-events/nih-research-matters.
[236] http://salud.nih.gov/.
[237] https://directorsblog.nih.gov/.

continue to expand their evidence-based public education and awareness campaigns directed at a variety of audiences.

Many campaigns focus on specific audiences for prevention and treatment efforts. Others concentrate on a specific behavioral health outcome, such as early diagnosis; decreased morbidity and mortality; family history, genetics, and genomics; infectious disease control and the need for vaccines; delivery of quality health care to people with special needs; diet and nutrition; and improved and refined health care practices. Several ICs sponsor clearinghouses for easy access to research-based materials. Examples of NIH health campaigns and clearinghouses are included throughout Chapter 3, and a listing of featured health awareness, prevention, and treatment campaigns sponsored by NIH is on the NIH website.[238]

Identifying Public Health Needs (Epidemiology)

The mission of NIH, along with the rest of the PHS, is to address ongoing and newly emerging public health needs. The 27 NIH ICs and OD collectively house expertise on a broad spectrum of diseases, populations, and research support methods. Large-scale epidemiological studies provide an ideal opportunity for researchers from various NIH components to work together on innovative studies that examine the frequency, pattern, and determinants of health events in a population. Our investments in epidemiology and public health continue to pay off as NIH contributes to the nation's ability to detect emerging and re-emerging diseases quickly, mitigate their health impacts, and improve the nation's resilience to future disease threats.

NIH Epidemiological Research Activities

Epidemiological studies examine the distribution of and the factors that contribute to health and disease in human populations using a broad range of approaches. Epidemiological research, a cornerstone of public health, helps us understand how many people have a disease or disorder, whether those numbers are changing, and how the disorder affects our society and our economy. Groups can be followed over time in longitudinal (cohort) studies, or a snapshot of information can be collected at a single point in time (cross-sectional studies). Studies can be done retrospectively, examining outcomes that already have occurred and factors that may have contributed to health or disease, or they can be done prospectively by beginning to monitor a population of interest before a particular disease-related outcome occurs. Epidemiological research can be experimental, but many epidemiological studies are observational in nature, collecting information about and comparing groups' individuals who share a characteristic of interest (e.g., tobacco use, age, educational status).

Providing major influence across the continuum from basic to applied research, epidemiological studies often test the findings of laboratory or clinical research at the population level. Additionally, observations

[238] http://www.nih.gov/icd/od/ocpl/resources/campaigns/.

made through epidemiological studies often result in the formulation of new or modified hypotheses that spur new basic, translational, and clinical studies. For example, epidemiological studies in the 1950s that showed that tobacco smoking increases the risk of lung cancer led to extensive research to identify the carcinogens and mechanisms involved. Epidemiological studies are essential for linking results from the bench to the patient's bedside to the general population.

Epidemiological research is important for investigating all types of disease and draws on expertise from a wide range of disciplines. It is not surprising that virtually all NIH ICs are involved with epidemiological research in some capacity, as illustrated in the examples of epidemiological research in Chapter 3.

Population Studies

Population studies are a type of epidemiological research aimed at better understanding how populations change in size, composition, and distribution; the complex social, economic, and cultural factors that cause such changes; and the consequences of population change for health and well-being at the individual and societal levels. The population-based perspective provided by such studies often helps establish a foundation for the practical application of scientific knowledge, including changes in clinical practice and the development of public policy. For example, the Framingham Heart Study, which was initiated in 1948, linked the risk of cardiovascular disease to such factors as high serum cholesterol levels, hypertension, and cigarette smoking. From these results, clinicians were able not only to identify patients at high risk for cardiovascular disease but also—even more important—to develop interventions that reduce risk.

Epidemiological Studies in Diverse Contexts

A comprehensive understanding of health and disease requires consideration of factors from the molecular to the community level. Conducting studies in diverse contexts helps clarify how these contributors converge to influence health and ensures that insights gained will benefit various populations. NIH supports a number of studies in the U.S. and worldwide aimed at building a comprehensive understanding of health and disease, with the goal of identifying new and more effective approaches for prevention and treatment (see Chapter 3 for examples).

Infrastructure, Research Resources, and Technology Development

Many of the core challenges in research today require technologies, databases, and other scientific resources that are more sensitive, robust, and easily adaptable to unique applications than what currently exists. NIH makes significant investments in the development of research infrastructure and resources, as well as state-of-the-art technologies to support its broad portfolio of research. Below is an overview of

NIH's focus on the development of research resources and technologies. Details on specific efforts are provided throughout Chapter 3.

Infrastructure and Research Resources

To ensure that research resources developed with NIH funding are made readily available to the research community for further study, NIH supports multiple repositories for the collection and dissemination of animal models, cell lines, and other vital biomedical research reagents. Repositories are updated continuously as resources become available; examples of NIH-funded repositories are included in Chapter 3.

Data are also a vital research resource. With continued advancements in high-throughput methods, the sheer volume of data collected has ballooned in recent years, requiring significant investment in systems to house and manage the data. To advance biomedical science, health, and health care, NIH has focused efforts on developing and deploying databases, disease registries, and other biomedical information systems:

- *Databases.* These databases archive and provide access to authoritative scientific literature, research data (including disease-specific data and genomic data), and clinical research information.
- *Disease registries and surveillance systems.* NIH supports the collection and curation of information about the occurrence of specific diseases and works with other federal and private entities to integrate disease registries for national and local use.
- *Information systems.* These information resources support collection, analysis, and storage of research data.

Specific examples of NIH's efforts in these three domains are provided in Chapter 3. Additionally, to comply with Section 403 (a)(4)(C)(ii) of the *PHS Act* to provide catalogs of disease registries and other data systems, Appendix G includes an inventory of NIH intramural and extramural activities ongoing in FY 2016, 2017 and 2018 to develop or maintain databases, disease registries, and other information resources for the benefit of the larger research community.

To make these and other data systems more useful to researchers, clinicians, and the public, NIH invests in a number of activities, including the following:

- *Standardized vocabularies and data protocols.* NIH leads the government's efforts to develop standardized vocabularies and terminology to support interoperability among biomedical information systems in research and clinical settings. NLM is designated as the central coordinating body for clinical terminology standards within HHS.

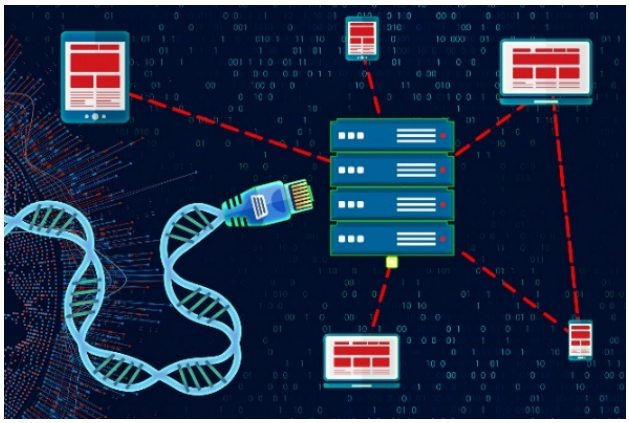

Figure 19. Schematic of data servers for genomic data. Credit: Ernesto Del Aguila III, NHGRI.

- *Large-scale informatics infrastructure.* NIH funds the development of large-scale systems and tools that allow communities of researchers to collect, share, visualize, and analyze data needed for research, clinical care (including electronic health records), and public health.
- *Biomedical informatics research and training.* NIH is the largest federal funder of biomedical informatics research, which aims to advance the applications of computing to biomedicine for both research and clinical care. NLM supports research in biomedical informatics and training for informatics researchers and information specialists.

The development, deployment, and utilization of biomedical information resources are essential to managing large amounts of data for research, clinical care, and public health—often referred to as Big Data. Increasingly, these technologies serve not only as repositories of information but also as research tools that can augment laboratory research. For example, scientists can use molecular databases to study the profiles of individual tumors and conceptualize small-molecule anticancer agents to target them. New analytical tools enable researchers to harness large datasets to address increasingly complex questions, such as how the expression patterns of multiple genes are associated with a particular trait or response. Such tools are most effective when databases are interoperable and capable of communicating with one another and make use of similar software applications. NIH is keenly attuned to the importance of and challenges associated with preserving, protecting, and ensuring the validity and security of information stored in biomedical databases.

Harnessing the power of the Internet creates unprecedented access to health care information in patient files, as well as to raw research data from clinical trials. For health science researchers, shared virtual libraries provide access to data and images from hundreds of studies in various fields. Devising the infrastructure to support a seamless end-user environment requires the collaboration of a host of professionals in computer science, medicine, information science, records management, and other related fields.

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support its mission. NIH databases and information systems,

particularly the more than 200 resources from NLM, have become indispensable national and international resources for biomedical research and public health. Several trans-NIH activities, including the BD2K initiative,[239] feature the development of significant biomedical information resources, including the tools, infrastructure, and associated research needed to make databases and registries more valuable.

As biomedical research becomes more data intensive, so do the challenges for researchers to release, locate, manage, analyze, and interact with these data in the discovery and application process. To capture the opportunities and address the challenges facing all biomedical researchers, NIH has launched initiatives to increase data sharing among scientists and support new methods of managing and analyzing complex and large datasets.

Figure 20. Genomic data sharing. Darryl Leja, NHGRI.

Technology Development

Technological advances move at an unprecedented pace. New technologies are needed, for example, to develop a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation; to develop a more precise knowledge of the combined effects of environmental exposures, individual susceptibility, and molecular events at the onset of disease; and to capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology. Moreover, widespread access to such tools will be essential for moving these fields forward.

NIH supports technology development through several complementary approaches, including—

- Research project grants directed at the development of a particular technology; some projects may take only a few years, while others may continue for a decade or more.

[239] https://commonfund.nih.gov/bd2k/index.

- Bioengineering research partnerships that bring together multiple disciplines in the physical and life sciences—such as engineering, cell biology, physics, and neuroscience—to develop solutions to specific biomedical questions or diseases.
- Specialized centers that represent a critical mass of expertise and technology, in which multidisciplinary development of complex, often unique technologies is pursued, typically in the context of challenging research problems that cannot be approached with existing tools.
- Small business grants through the SBIR and STTR programs for highly innovative projects to bring technological advances into the marketplace for the broadest possible availability and impact. These programs allow NIH to leverage the unique resources and perspectives available in the private sector to complement the work done at universities and the NIH IRP.
- High-risk, innovative projects with little preliminary indication of the likelihood of success but that could have a deeply significant impact if successful. Such proof-of-principle projects usually have small budgets and short time frames.

Summary

As the nation's medical research agency, NIH supports a continuum of research—from basic to preclinical translational to clinical to postclinical translational—driving the development of new technologies and important discoveries that will improve health and save lives. NIH research focuses on both ongoing and newly emerging public health needs, many of which are identified through population-based epidemiological research. This research would not be possible without NIH's strong focus on developing and maintaining research resources and infrastructure.

This chapter provided an overview of the component parts of this research continuum. Chapter 3 presents updates on key NIH activities across this research continuum in FY 2016, 2017, and 2018.

Chapter 3 NIH Research Activities in FY 2016, 2017, and 2018

Building on the overview of NIH and the research continuum it supports, as laid out in Chapters 1 and 2, this chapter presents a cross-section of some of NIH's research activities from the FY 2016, 2017, and 2018 reporting period. Many of the topics addressed are categories specified in the *PHS Act* (see Appendix A) and are grouped together in one chapter to address the intent of the statute, in terms of presenting information on diseases, disorders, and adverse health conditions in a standardized format.

Cancer

Cancer research is leading to improved cancer prevention, screening, and treatment. Substantial progress has been made to reduce the burden of cancer, reflected by decreasing cancer mortality death rates and increasing numbers of cancer survivors, yet cancer continues to have a major impact on society.[240] In the U.S., approximately 38.4 percent of men and women will be diagnosed with cancer at some point during their lifetimes.[241] In 2017, an estimated 15,270 children and adolescents from birth to age 19 were diagnosed with cancer, and 1,790 died of the disease. Estimated national expenditures for cancer care in the U.S. in 2017 were $147.3 billion. In future years, costs are likely to increase as the population ages and cancer prevalence increases.

Jointly issued by the CDC, the North American Association of Central Cancer Registries, American Cancer Society, and NCI, *The Annual Report to the Nation on the Status of Cancer* reports on rates for new cancer cases and deaths, as well as trends for the most common cancers in the U.S.[242] The 2018 report covered the years 1975–2015. According to this report, researchers found continued declines in cancer mortality rates for men, women, and children.[243] Overall cancer incidence rates (numbers of new cases of cancer per 100,000 people in the U.S.) continued to decrease among men and remained stable among women. From 2010 to 2014, incidence rates during the most recent 5-year period decreased for 7 of the 17 most common cancer types among men (prostate, lung and bronchus, colorectal, bladder, esophagus, brain, and other nervous system). Among women, incidence rates declined for 7 of the 18 most common cancers (lung and bronchus, colorectal, non-Hodgkin's lymphoma, ovary, bladder, cervix, and brain and other nervous system) over this period. The report found that differences in rates and trends by race and ethnic

[240] Cronin KA, et al. *Cancer* 2018;124(13):2785-800. PMID: 29786848.
[241] https://www.cancer.gov/about-cancer/understanding/statistics.
[242] https://seer.cancer.gov/report_to_nation/.
[243] Cronin KA, et al. *Cancer* 2018;124(13):2785-800. PMID: 29786848.

group remain. For all cancer sites combined, Black men and Black women had the highest death rates compared with other racial groups. Each year's report also includes a special section that describes trends and disease characteristics in a specific topic, such as liver cancer incidence (2016),[244] cancer survivorship (2017),[245] or prostate cancer (2018).[246]

Summary of NIH Activities

NCI leads the agency's cancer research efforts; however, many other NIH ICs conduct and support cancer-related research, including the CC, NCATS, NHGRI, NHLBI, NIA, NIAID, NIAMS, NICHD, NIEHS, NINR, NIGMS, and the NIH Common Fund. NIH supports research on the molecular basis of cancer, risk factors, prevention, screening and diagnosis, treatment, and survivorship, as well as the development of cancer research infrastructure and collaborations. Total NIH funding for cancer research was $5.589 million in FY 2016, $5.980 million in FY 2017, and $6.335 million in FY 2018.[247] NIH has played a major role in the progress made by the cancer community, but more still needs to be done to reduce the burden of cancer for patients, families, and society. To accomplish this, work needs to span the research continuum, from studies of basic biology to examination of cancer rates across the population. NIH support of this broad research agenda can be seen in key initiatives from FY 2016–2018, such as the Cancer Moonshot Initiative and its implementation of the Blue Ribbon Panel recommendations. In addition, *The Cancer Trends Progress Report,* in response to Healthy People targets set by HHS, measured progress along the cancer control continuum in relation to cancer survivors and smoking, obesity, and physical activity (2016); human papillomavirus (HPV) immunization (2016); and the financial burden of cancer care (2017).[248]

Recalcitrant Cancer Research

In response to the mandate under Sec. 417G (d)(1) of the *PHS Act* to provide information on actions taken to implement scientific frameworks developed with respect to recalcitrant cancer, Appendix H includes the following information on pancreatic ductal adenocarcinoma and small cell lung cancer research:

- Information on FY 2016, 2017, and 2018 grants funded
- Assessment of progress in these research fields
- Update on activities in these research fields

Understanding the Biology

Cancer is a genetic disease—meaning that cancer is caused by certain changes to genes (such as mutations) that control the way our cells function, especially how they grow and die. Certain gene changes can cause cells to evade normal growth controls and become cancer. Genetic changes that promote

[244] Ryerson AB, et al. *Cancer* 2016;122(9):1312-37. PMID: 26959385.
[245] Jemal A, et al. *J Natl Cancer Inst* 2017;109(9). PMID: 28376154.
[246] Negoita S, et al. *Cancer* 2018;124(13):2801-14. PMID: 29786851.
[247] https://report.nih.gov/categorical_spending.aspx.
[248] https://progressreport.cancer.gov/.

cancer can be inherited from our parents if the changes are present in germ cells, which are the reproductive cells of the body (eggs and sperm). Such changes, called germline changes, are found in every cell of the offspring. Cancer-causing genetic changes can also be acquired during one's lifetime, as the result of errors that occur as cells divide or from exposure to carcinogenic substances that damage DNA, such as certain chemicals in tobacco smoke, and radiation, such as ultraviolet rays from the sun. Genetic changes that occur after conception are called somatic (or acquired) changes. One of the most significant challenges facing cancer researchers is dissecting the ways in which these changes can turn normal, healthy cells into cancer cells.

Cells of Origin and Cancer Classification

The way a cancer cell behaves is attributed in part to the cell of origin, or the tissue where a cancer developed, and cancers are classified by where they developed in the body. Broadly speaking, cancers can be grouped according to the types of cells that they originate in, such as skin or tissue linings of organs (carcinoma); connective or supportive tissues like bone, cartilage, muscle, or blood vessels (sarcoma); bone marrow and blood (leukemia); immune system (lymphomas and myelomas); or the brain and spinal cord.

Cancers that originated from different cell types may have different patterns of gene expression. At the same time, scientists have found that certain mutations may occur in many types of cancer. Because of this, cancers may also be classified by the genetic alterations that are believed to be driving them. Cancer classification is important because different treatments may be recommended depending on the cancer type. Better cancer classification could help explain why some patients with the disease respond to treatment and others do not.

Carcinomas are the most commonly diagnosed cancers and originate in the skin, lungs, breasts, pancreas, and other organs and glands. Major types of carcinomas differ based on whether the cells contain certain cell-signaling molecules. For example, breast cancer is defined by the expression, or the lack thereof, of the estrogen and progesterone receptors, and by the abundance of another signaling molecule, the human epidermal growth factor receptor 2 (HER2). Breast cancers that lack expression of estrogen, progesterone, and HER2 receptors are referred to as triple negative breast cancers. Triple negative breast cancers that lack androgen receptor (AR) expression are considered "quadruple negative," and there is increasing evidence that AR expression has prognostic usefulness in triple negative breast cancer. Researchers analyzed AR expression across breast cancer subtypes and among African Americans and Whites.[249] Overall, AR-negative patients were diagnosed at a younger age than AR-positive patients. AR-negative patients were more likely to have a basal-like subtype, which is associated with a more quickly progressing disease and decreased overall survival. Thus, AR expression could be used as a prognostic marker for breast cancer to estimate the chance of recurrence, particularly in African American patients.

[249] Davis M, et al. *PLoS One* 2018;13(6). PMID: 29912871.

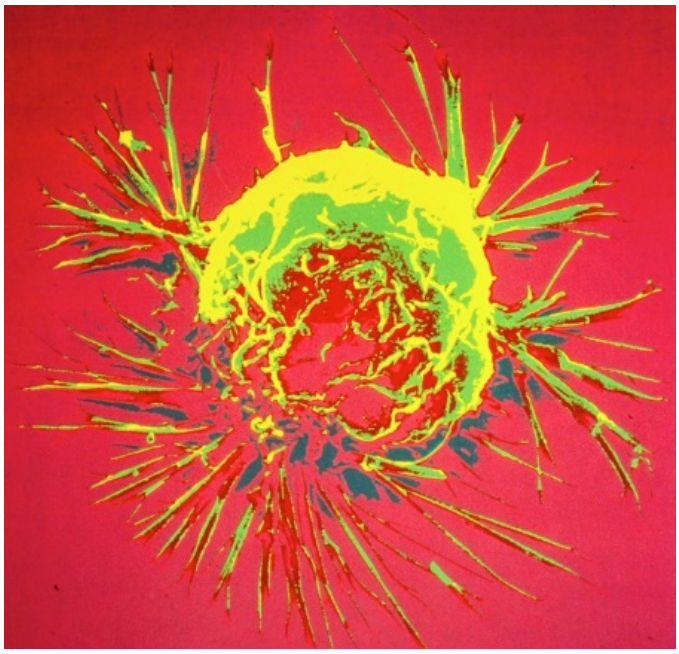

Figure 21. A breast cancer cell photographed by a scanning electron microscope. Credit: Bruce Wetzel and Harry Schaefer, NCI.

Advanced pancreatic ductal adenocarcinoma is characterized by poor prognosis, with a median survival time of less than 12 months. In 2018, two studies characterized advanced pancreatic cancer by identifying genomic expression signatures that could be used to identify targeted therapies and predict responses to treatment.[250,251] The hope is that studies like these will enable precision medicine for pancreatic cancer.

Liver cancer is the second leading cause of cancer death worldwide and includes hepatocellular carcinoma, which originates from the liver's primary cells, hepatocytes, and the less common intrahepatic cholangiocarcinoma, which develops from the cells that line the bile ducts, cholangiocytes. Traditionally, these have been described as two different cancer types with different clinical guidelines and different treatment recommendations. In 2017, a comprehensive molecular analysis of both cancers identified common molecular subtypes that can be found among patients with either disease.[252] Although they are considered separate diseases, this finding suggests that a unified clinical approach could benefit patients with both types of liver cancer.[253]

Sarcomas are cancers that arise from connective or supportive tissues like bone, cartilage, muscle, and blood vessels. Fusion oncoprotein-negative rhabdomyosarcoma is a pediatric cancer that was thought to originate from skeletal muscle progenitor cells. However, in 2018, researchers showed that endothelial

[250] Aung KL, et al. *Clin Cancer Res* 2018;24(6):1344-54. PMID: 29288237.
[251] Aguirre AJ, et al. *Cancer Discov* 2018;8(9):1096-1111. PMID: 29903880.
[252] Chaisaingmongkol J, et al. *Cancer Cell* 2017;32(1):57-70. PMID: 28648284.
[253] https://ccr.cancer.gov/news/article/molecular-profiles-suggest-two-types-of-liver-cancer-should-be-treated-as-one.

progenitor cells, which develop into blood vessel cells, can give rise to this type of sarcoma through abnormal activation of a particular cell signaling pathway, known as the Hedgehog pathway.[254]

Cancers can originate from the cells of the immune system, which circulate throughout the body in blood or lymph fluid. Diffuse large B-cell lymphoma is the most common type of cancer that originates from lymphocytes in the immune system. Although it can be aggressive, it is potentially curable, but researchers still do not have a full understanding of why only some cases respond to treatment. Now researchers have identified four prominent genetic subtypes that each share a group of genetic aberrations.[255,256] Patients with two of the subtypes, called BN2 and EZB, respond well to treatment, while those with the other two, MCD and N1, do not. In the future, precision medicine clinical trials could test these lymphomas for the new genetic subtypes, and then, based on the classification, the patient would be assigned to the most appropriate treatment arm of the study.

Another cancer of the immune system, multiple myeloma originates from antibody-producing plasma cells. Multiple myeloma is often preceded by a premalignant stage called smoldering multiple myeloma. Researchers provided a comprehensive description of the genomic features of smoldering multiple myeloma and modeled the disease progression to multiple myeloma.[257] The goal is to combine these genomic features with clinical and biological criteria to provide a more accurate risk stratification for patients to time treatment initiation in the smoldering stage and, ultimately, improve outcomes.

Benign (not malignant or cancerous) tumors can still cause complications for patients. Paragangliomas are a type of tumor that forms near certain blood vessels and nerves and are often benign. Studying data from more than 700 patients with paragangliomas, researchers found that children were more likely than adults to carry mutations in tumor susceptibility genes, or regions of DNA where genetic changes predispose a person to develop these tumors.[258] These differences can guide patient care for adults or children with tumors that originate near vessels or nerves.

Comparing the molecular characteristics of different cancers can lead to a better understanding of their similarities and differences and an improved classification of cancers, which can be used to develop new treatments or identify treatments that are likely to be effective for an individual patient or group of patients. NIH is a leader in the field, establishing large publicly available databases with highly contextualized data and clinical outcomes that can help researchers find novel treatments and interventions for many cancers.

In 2018, researchers funded by NCI and NHGRI published a series of 27 research papers from the PanCancer Atlas project, a cross-cancer-type analysis of The Cancer Genome Atlas (TCGA) and corresponding clinical information.[259] The findings from this project were divided into three main

[254] Drummond CJ, et al. *Cancer Cell* 2018;33(1):108-24. PMID: 29316425.
[255] https://www.cancer.gov/news-events/press-releases/2018/lymphoma-genetic-subtypes.
[256] Schmitz R, et al. *N Engl J Med* 2018;378(15):1396-1407. PMID: 29641966.
[257] Bolli N, et al. *Nat Commun* 2018;9(1):3363. PMID: 30135448.
[258] Pamporaki C, et al. *J Clin Endocrinol Metab* 2017;102(4):1122-32. PMID: 28324046.
[259] https://www.cell.com/pb-assets/consortium/pancanceratlas/pancani3/index.html.

categories: (1) cell-of-origin patterns, related to where in the body cancer develops; (2) oncogenic processes, related to how cancer develops; and (3) cell signaling pathways, related to how cells communicate with each other. Three of the 27 papers summarize the findings in each category.[260–262] Researchers analyzed more than 11,000 samples from 33 of the most prevalent forms of cancer. Overall, these findings will aid in the development of new treatments, including immunotherapies (a type of therapy that modulates the immune system to help the body fight disease), for a wide range of cancers.

The pediatric equivalent of TCGA—the NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative—applies a comprehensive genomic approach to determine molecular changes that drive childhood cancers to better match patients with effective treatments.[263] TARGET project teams study primarily high-risk leukemias and solid cancers, including osteosarcoma, neuroblastoma, and kidney cancer. Many of these cancers do not respond to standard treatments or typically return after a period of response. Results from this large-scale molecular characterization and sequencing initiative are made broadly available to the research community through the NCI Genomic Data Commons (GDC) to promote discovery.[264] In 2017 and 2018, three publications from TARGET advanced understanding of the genomics of childhood cancers.[265–267]

The NIH Common Fund's Gabriella Miller Kids First Pediatric Research Program is developing a large-scale data resource to help researchers uncover new insights into the biology of childhood cancer and structural birth defects.[268] These diseases and disorders have profound, lifelong effects on patients and their families. The Kids First program works toward providing a better understanding of how genetics plays a role in these conditions, which could lead to early detection, therapeutic interventions, and more effective prevention. NICHD—which co-chairs the Kids First Working Group along with NCI, NHGRI, and NHLBI—has long supported research on birth defects and has an overall focus on improving pediatric health. In September 2018, the Kids First Data Resource Center launched the Kids First Data Resource Portal, a centralized database of well-curated clinical and genetic sequence data from patients with childhood cancer or structural birth defects and their families.[269] The portal includes sequence data from approximately 8,000 DNA and RNA samples and is expected to grow to 30,000 samples over the next few years.

The International Cancer Proteogenome Consortium (ICPC) is a collaborative effort among more than 12 countries to study commonly diagnosed cancers in their unique populations with the goal of creating a cancer atlas representative of the diversity of cancers around the world. All molecular data (genomics, proteomics, imaging) and assays are made available to the public as a community resource to accelerate

[260] Hoadley KA, et al. *Cell* 2018;173(2):291-304. PMID: 29625048.
[261] Ding L, et al., *Cell* 2018;173(2):305-20. PMID: 29625049.
[262] Sanchez-Vega F, et al., *Cell* 2018;173(2):321-337. PMID: 29625050.
[263] https://ocg.cancer.gov/programs/target.
[264] https://gdc.cancer.gov/.
[265] Gadd S et al. *Nat Genet* 2017;49(10):1487-94. PMID: 28825729.
[266] Bolouri H et al. *Nat Med* 2018;24(1):103-12. PMID: 29227476.
[267] Ma X et al. *Nature* 2018;555(7696):371-6. PMID: 29489755.
[268] https://commonfund.nih.gov/kidsfirst.
[269] https://kidsfirstdrc.org.

cancer research and advance patient care. Launched in 2016 and inspired by the Cancer Moonshot, ICPC facilitates international cooperation to represent the international diversity of populations, of people, and of cancers.

Mechanisms of Cancer Development and Progression

New imaging and genetic technologies developed during the past decade have helped researchers examine the structure and function of genetic alterations that underlie both normal biological processes and aberrant ones, such as those that lead to the development of cancer. These tools have also been used to study mechanisms of DNA damage and repair, gene regulation and expression, and drug binding in cancer cells. Knowledge gained from such studies deepens our understanding of cancer and produces insights that could lead to the development of new clinical interventions and improvements to current treatments.

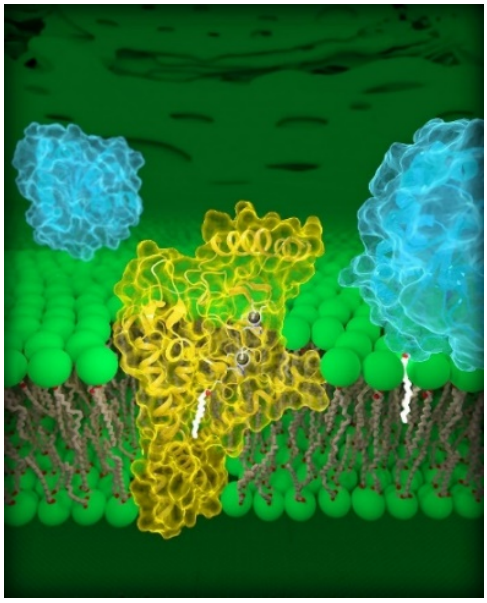

Figure 22. 3-D diagram of the molecular view of the DHHC palmitoyltransferases enzyme. Human DHHC20 (yellow) is embedded in the Golgi membrane (green), a compartment located inside cells. DHHC20 attaches a fatty acid chain (white) to a target protein (blue, foreground), which anchors the protein to the Golgi membrane. Credit: Jeremy Swan, NICHD.

Three-dimensional (3-D) structures of biomolecules provide a wealth of information on their biological function and evolutionary relationships. NICHD-supported scientists have reported the first 3-D structure of DHHC proteins, which are enzymes involved in many cellular processes, including cancer.[270,271] This structure explains how these proteins function and may offer a blueprint for designing therapeutic drugs. These proteins modify other proteins by attaching a chain of lipids, or fatty acids, of varying lengths. Researchers estimate that nearly 1,000 human proteins undergo this process, including the epidermal growth factor receptors that can be overactivated in certain types of cancer. Researchers have proposed

[270] Rana MS, et al. *Science* 2018;359(6372). PMID: 29326245.
[271] https://www.nih.gov/news-events/news-releases/nih-researchers-report-first-3d-structure-dhhc-enzymes.

blocking DHHC activity to boost the effectiveness of first-line treatments against common forms of lung and breast cancer. However, currently no licensed drugs target specific DHHC enzymes. Determining the enzyme structure is a new starting point to develop drugs that can influence enzyme activity.

Understanding molecular interactions, as well as structure, can aid in drug development for cancer and many other diseases. In 2016, NCI Center for Cancer Research investigators developed a groundbreaking new technology based on cryo-electron microscopy (cryo-EM) to visualize the atomic structures of proteins.[272] The researchers used this technique to view the binding of a potential small-molecule drug to a key protein in cancer cells. The images also helped the researchers establish the sequence of structural changes that normally occur in the protein p97, an enzyme critical for protein regulation that is thought to be a novel anticancer target.[273] Cryo-EM maps that show the contacts between small molecules and proteins will help explore questions such as why one drug is better than another or why certain drugs fail.[274] This method can benefit biomedical research beyond the study of cancer. In 2018, this group captured a series of highly detailed images that revealed new insights on how the CRISPR/Cas9 gene editing complex works.[275]

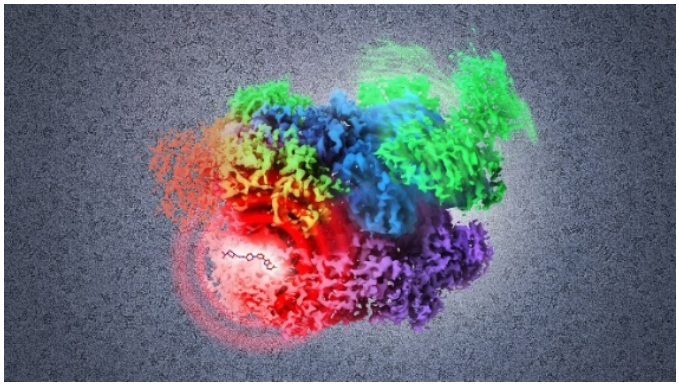

Figure 23. Image of the protein p97 trapped in an inactive state by a new inhibitor (red), created using cryo-electron microscopy. Credit: NCI.

Genomic instability, originating from the germline (inherited) or somatically (acquired after conception), is a significant step in the initiation or progression of a cell to cancer. DNA repair mechanisms are a major defense against genomic instability and damage to cells and are present in the cells of all organisms. An important and dangerous type of DNA damage is known as a DNA-protein crosslink. This type of damage generates breaks in the genome. If these breaks are not removed, they trigger cell death. Some chemotherapies exploit this vulnerability, inducing the formation of DNA-protein crosslinks to kill cancer cells. At the same time, DNA-protein crosslinks also can be the source of disease, as they can cause rearrangement of an organism's genome that leads to cancer. Recently, an international team led by scientists at NIH was the first to discover a new way that cells fix DNA-protein crosslinks.[276] The

[272] https://www.nih.gov/news-events/news-releases/cancer-drug-target-visualized-atomic-resolution.
[273] Banerjee S, et al. *Science* 2016;351(6275):871-5. PMID: 26822609.
[274] Merk A, et al. *Cell* 2016;165(7):1698-1707. PMID: 27238019.
[275] Guo TW, et al. *Cell* 2017;171(2):414-26. PMID: 28985564.
[276] https://www.niehs.nih.gov/news/newsroom/releases/2017/october6/index.cfm.

researchers found that the protein ZATT can eliminate DNA-protein crosslinks with the help of another protein, TDP2.[277] Understanding how TDP2 and ZATT work together to repair the damage may improve the health outcomes of cancer patients.

Certain chemicals are known to induce DNA damage and cause cells to divide rapidly, which can lead to cancer. People with Down syndrome are typically less likely than the general population to develop solid cancers. However, after being exposed to certain cancer-promoting chemicals, mice bred to mimic the genetic basis of Down syndrome were more likely to develop hyperkeratosis (a thickening of the skin) and papillomas (wart-like skin growths) than their genetically unaffected littermates.[278] These experiments suggest that changes in gene expression in Down syndrome may be responsible for the growth and overgrowth of certain types of cells. Understanding this may help us treat certain symptoms of Down syndrome, as well as provide insights into some aspect of cancer cell growth.

A recent study demonstrated that pediatric cancers may be genetically distinct from their adult counterparts.[279] This study examined Ewing sarcoma, which occurs primarily in children and young adults and forms in the bones or the soft tissue around bones. Eighty-five percent of Ewing sarcomas are driven by a fusion oncoprotein (EWS-FLI1), which is the result of the fusion of pieces of two genes into one. The activity of this fusion protein drives cancer growth. Recent findings revealed that EWS-FLI1 increases gene expression and DNA damage, while simultaneously reducing a cell's ability to repair damaged DNA through a process called homologous recombination. Notably, in this study, the researchers identified the protein BRCA1 as a key player in the impairment of homologous recombination. (A person who inherited mutations in the gene *BRCA1* has a higher risk of getting breast, ovarian, prostate, and other types of cancer.) These findings enhance our understanding of the molecular mechanisms that drive pediatric cancers.

Rhabdomyosarcoma is another form of a cancer that occurs mainly in children. The most common mutations found in these cancers occur in members of the *RAS* gene family (*NRAS*, *HRAS*, or *KRAS*). These mutations are acquired early and are thought to drive cancer development. Researchers in the NIH IRP identified a new therapeutic target for this disease.[280] In this study, the researchers showed that these cancers may be susceptible to drugs that target MEK, a protein in a shared cell signaling pathway of all three *RAS* family members.[281] This new understanding led the researchers to test a drug to inhibit MEK in an animal model. The findings showed that the drug might be a good candidate to test in clinical trials for this disease.

Immunological Defenses Against Cancer

Within a cancer mass, the cancer cells are surrounded by a variety of other cell types, including immune cells. The immune system is a network of specialized cells, tissues, and organs that protects the body from

[277] Schellenberg MJ, et al. *Science* 2017;357(6358):1412-16. PMID: 28912134.
[278] Yang A, et al. *PLoS One* 2016;11(1). PMID: 26752700.
[279] Gorthi A, et al. *Nature* 2018;555(7696):387-91. PMID: 29513652.
[280] https://ccr.cancer.gov/news/article/blocking-mek-signaling-pathway-could-inhibit-rhabdomyosarcoma-growth.
[281] Yohe ME, et al. *Sci Transl Med* 2018;10(448). PMID: 29973406.

infections and other diseases. The immune system has evolved to detect non-self or foreign threats, such as bacteria and viruses, but it is harder for it to detect and attack cancer cells because they are not seen as foreign. Cancer cells can hide from or thwart an attack. Some cancer treatments, called immunotherapies, help the immune system better detect and kill cancer cells.

Cancer immunotherapy relies on T cells, a type of immune cell, to kill individual cancer cells and ultimately destroy cancers. However, some cancer cells are resistant to the destruction unleashed by T cells. A study led by investigators from the NCI IRP identified more than 100 genes in cancer cells that may play a role in avoiding death by T cells.[282,283] The list of genes generated from this study could serve as a blueprint to study the emergence of cancer resistance to T cell–based immunotherapies.

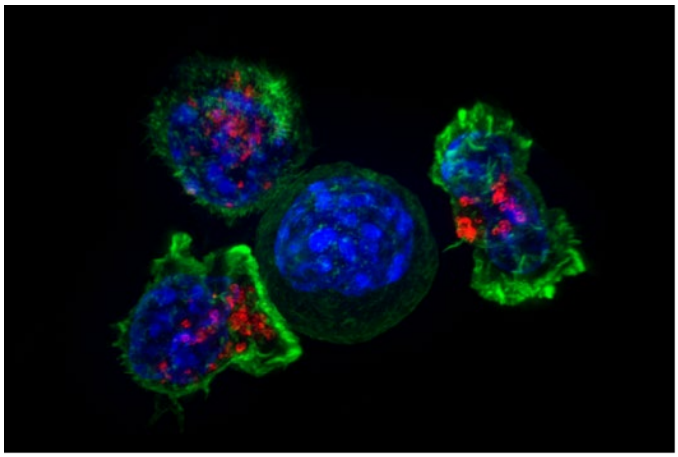

Figure 24. Immunofluorescence image of a group of killer T cells (green and red) surrounding a cancer cell (blue, center). When a killer T cell makes contact with a target cell, the killer cell attaches and spreads over the dangerous target. The killer cell then uses special chemicals housed in vesicles (red) to deliver the killing blow. This event has thus been nicknamed "the kiss of death." After the target cell is killed, the killer T cells move on to find the next victim. Credit: Alex Ritter, Jennifer Lippincott Schwartz, and Gillian Griffiths, NIH.

Chronic liver inflammation can lead to liver cancer, the second leading cause of cancer deaths around the world. Researchers have long thought that the progression to cancer happens because inflammation stimulates cell division and protects from cell death. Researchers have now found that chronic liver inflammation also promotes cancer by suppressing immunosurveillance—a natural defense mechanism in which the immune system identifies pre-cancerous and cancer cells and shuts down cancer development.[284,285] This research provides evidence that the adaptive immune system—through activated T cells surveying the body—plays an active role in liver cancer prevention.

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors, a new class of drugs first approved by FDA in 2015, have been shown in breast cancer patients to increase the amount of time before their disease progresses. These drugs block the activity of two proteins, CDK4 and CDK6, that help to control cell division. In recent

[282] https://www.cancer.gov/news-events/press-releases/2017/immunotherapy-genes-study.
[283] Patel SJ, et al. *Nature* 2017;548(7669):537-42. PMID: 28783722.
[284] https://health.ucsd.edu/news/releases/Pages/2017-11-08-how-chronic-inflammation-tips-the-balance-to-promote-liver-cancer.aspx.
[285] Shalapour S, et al. *Nature* 2017;551(7680):340-45. PMID: 29144460.

research using mouse models, investigators identified how these molecules turn off cell division. The researchers confirmed their findings in biopsies from breast cancer patients treated with CDK4/6 inhibitors.[286] CDK4/6 inhibitors increased immunogenicity, or the ability of the cancer cells to provoke an immune response. These findings provide a rationale for new treatment combinations with CDK4/6 inhibitors and immunotherapies, such as checkpoint inhibitors (a class of drugs that release molecular brakes on the immune system and enable T cells to detect and kill cancer cells better).

Researchers are also investigating the role of metabolites (substances made when the body breaks down food or other molecules) in the interaction between cancer and the immune system. In 2016, NCI held a workshop to examine the modulation of anticancer immune responses by metabolites derived from diet and the microbiome—the community of microorganisms that inhabit the human body.[287] The workshop identified some of the critical gaps and research challenges that could be addressed through interdisciplinary collaborations, including future opportunities for translating new information into novel cancer prevention and treatment strategies based on targeting host immune functions that are altered by metabolite-sensing pathways.

As part of the Cancer Moonshot Initiative and the Cancer Immunotherapy Consortium (CIC), NIDCR is leading two studies to better understand how head and neck squamous cell cancers (HNSCC) evade immune system detection to develop better treatments. One group of scientists is searching for ways to enhance the effectiveness of treatment by combining radiation therapy and immunotherapy. Their approach is to identify and precisely target the inflammatory signals that HNSCC tumors use to resist chemoradiotherapy.[288] Another group is determining how cancer neoantigens—molecules that have been mutated within the tumor—can be manipulated so the immune system can recognize them. Using a variety of novel preclinical tools, they will identify and characterize new HNSCC neoantigens that will improve existing immunotherapeutic options and lead to new targeted therapies.[289]

Improved understanding of the interaction between cancer cells and the immune system shines a spotlight on the biological complexity associated with cancer. Cancer systems biology is uniquely poised to address this complexity through its unique integration of experimental biology and computational and mathematical analysis. In systems biology, researchers use this integrated approach to describe the complex interactions among components of a biological system and make predictions that help guide and further refine experimental science. The Cancer Systems Biology Consortium (CSBC) was launched in FY 2016. The overall research themes of CSBC address important questions in basic cancer research, including the emergence of drug resistance, the mechanisms underlying cancer metastasis, and the role of the immune system in cancer progression and treatment.[290] CSBC interdisciplinary investigators integrate experimental biology with mathematical and computational modeling to gain insight into processes relevant to cancer initiation, progression, and treatment options.

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[286] Goel S, et al. *Nature* 2017;548(7668):471-5. PMID: 28813415.
[287] Kumar A et al., *J Natl Cancer Inst* 2017;109(6). PMID: 30053241.
[288] https://projectreporter.nih.gov/project_info_description.cfm?aid=9625949&icde=43126044.
[289] https://projectreporter.nih.gov/project_info_description.cfm?aid=9626324&icde=43126069.
[290] https://www.cancer.gov/about-nci/organization/dcb/research-programs/csbc.

Identifying Risk Factors

It is usually not possible to know exactly why one person develops cancer and another does not, but research has shown that certain risk factors may increase a person's chances of developing cancer. Cancer risk factors include exposure to cancer-causing substances, certain behaviors, age, and inherited genetic mutations. Studying the causes of cancer helps researchers understand the process of carcinogenesis and identify genetic, environmental, and behavioral risk factors for cancer. This knowledge can lead to new ways of preventing and treating the disease.

Researchers use epidemiological approaches to identify possible causes of cancer and study the patterns of risk in large populations. In cohort studies, scientists look at large groups of people and compare those who develop cancer with those who do not. Additionally, characterizing trends in cancer incidence and mortality within a given population—and between populations over time—yields clues that may point researchers to cancer causes and risk factors.

Cancer affects people of all races and ethnicities in the U.S.; however, the burden is greater for certain populations. For example, African American/Black women are more likely to die from breast cancer despite White women's having higher incidence rates for the disease. Recent reports of converging Black and White breast cancer incidence rates have gained attention, potentially foreshadowing a worsening of the Black–White breast cancer mortality disparity. It is important to note that these incidence rates also reflect the sum of non-Hispanics and Hispanics, which may mask important racial- and ethnic-specific trends. Investigators examined breast cancer incidence trends among non-Hispanic White women, Hispanic White women, and non-Hispanic Black women in the NCI Surveillance, Epidemiology, and End Results (SEER) 13 Registries Database.[291] They used statistical modeling of breast cancer trends to predict incidence rates for 2015–2030, and projected slowly increasing incidence rates for non-Hispanic White and Hispanic White women and slowly decreasing rates for non-Hispanic Black women. The investigators concluded that a worsening of the Black–White racial mortality gap seems unlikely; however, they call for continued monitoring of race- and ethnic-specific breast cancer trends by age and disease characteristics to learn more about what causes disparities in incidence and to develop targeted prevention strategies.

Two recent studies put a spotlight on rural cancer disparities. The studies—one by NCI researchers[292] and one led by CDC researchers using NCI SEER data[293]—showed that, compared with people living in urban areas, those residing in rural areas experience a lower incidence of cancer but a higher cancer mortality rate. In addition, the decreases in cancer mortality rates observed in recent years have been smaller in rural areas than in urban areas.

Previous epidemiologic studies have found that individuals with benign thyroid conditions—such as nodules, adenomas (non-cancerous tumors), goiter (swelling in the neck resulting from an enlarged thyroid gland), functional thyroid diseases (hyperthyroidism and hypothyroidism), and thyroid-specific

[291] Davis Lynn BC, et al. *J Natl Cancer Inst* 2018;110(11):1270-72. PMID: 29982593.
[292] Blake KD, et al. *Cancer Epidemiol Biomarkers Prev* 2017;26(7):992-7. PMID: 28600296.
[293] Henley SJ, et al. *MMWR Surveill Summ* 2017;66(14):1-13. PMID: 28683054.

autoimmunity—have a higher risk of thyroid cancer. However, it is unclear whether these relationships are causal or due only to greater opportunity for incidental detection of thyroid cancer. Investigators within NCI's intramural research program and collaborators prospectively examined a wide range of benign thyroid conditions and risk of differentiated thyroid cancer and found that goiter, adenoma, hyperthyroidism (but not hypothyroidism), and thyroiditis (inflammation of the thyroid gland) were associated with a long-term increased risk of thyroid cancer.[294,295] This work provides important new evidence on risk factors for thyroid cancer.

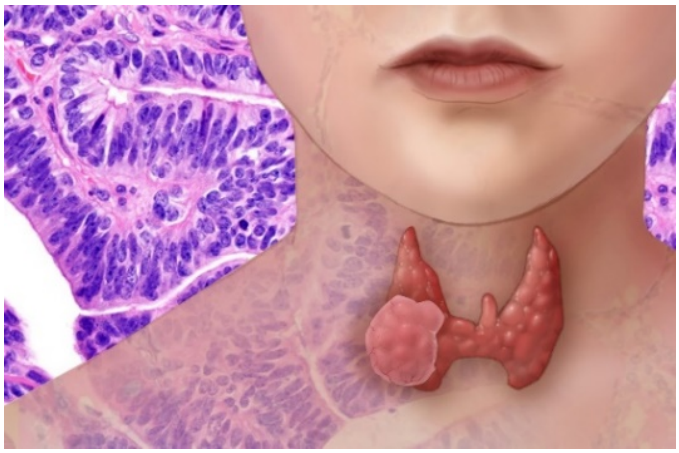

Figure 25. Although thyroid cancer is very treatable with surgery and other therapies, it remains the fastest growing cancer in the United States. Credit: Darryl Leja, NHGRI.

Genetic Risk Factors

Certain risk factors are out of one's control, like age, family history, and genetics. Changes in an individual's genes—including gene mutations, genetic modifiers, and polymorphisms—can alter one's lifetime risk of cancer. A family history of certain cancers can be a sign of a possible inherited cancer syndrome. Genetic analyses—such as GWAS, exome sequencing, and whole-genome sequencing—allow researchers to identify inherited genetic differences, or variants, that may be associated with cancer risk. NIH researchers are studying genetic factors and gene–environment interactions that may predispose individuals to cancer using these approaches.

For example, NCI's Genetic Associations and Mechanisms in Oncology (GAME-ON) initiative and its spin-off project, the OncoArray Network, include collaborators from around the world at more than 350 institutions in 60 countries who conduct research on cancer genetic risk factors.[296] In 2017 and 2018, new genetic susceptibility variants—or genetic alterations that increase an individual's predisposition to

[294] https://dceg.cancer.gov/news-events/news/2018/benign-thyroid.
[295] Kitahara CM, et al. *J Clin Endocrinol Metab* 2018;103(6):2216-24. PMID: 29590402.
[296] https://www.cancer.gov/news-events/cancer-currents-blog/2018/oncoarray-genetic-variants-cancer-risk.

cancer—were published for lung,[297] breast,[298,299] and prostate[300] cancers. With this information in hand, researchers may be able to identify specific groups of people who might benefit most from earlier screening for a given cancer or who might safely put off screening for a few years.

Researchers recently associated specific regions of the genome—called genetic loci—with risk of developing renal cell carcinoma, the most common type of kidney cancer. There is a known twofold increased risk of renal cell carcinoma in first-degree relatives of renal cell carcinoma patients, which may indicate a possible inherited cancer syndrome. While an inherited predisposition to this type of kidney cancer is linked to some rare cancer syndromes, it accounts for only a small portion of renal cell carcinoma cases. Researchers conducted a GWAS to validate six previously identified risk loci and identify seven new loci associated with renal cell carcinoma.[301] These findings provide important new leads into the biologic pathways affecting kidney cancer development.

A recent GWAS identified multiple regions of the genome that are associated with risk of the pediatric cancer, Ewing sarcoma. This study validated three previously known genetic susceptibility loci and identified three new risk loci, in addition to the presence of the known fusion oncoprotein EWSR1-FL1 that drives the development of Ewing sarcoma.[302] Although the EWSR1-FLI1 fusion is acquired during development rather than inherited, this study provides evidence for a strong inherited genetic component to Ewing sarcoma. The results also suggest that inherited and acquired mutations may interact to increase Ewing sarcoma risk.

Investigators from the NCI-supported Barrett's Esophagus Translational Research Network (BETRNet) identified the first genetic risk factor for acquiring familial Barrett's esophagus and esophageal cancer. The gene, *VSIG10L*, normally helps to maintain a healthy esophagus, but a rare hereditary mutation could turn it into a risk factor for familial Barrett's esophagus. This research generated new knowledge about how this disease develops and suggests that individuals carrying this mutation would benefit from early screening and close clinical monitoring.

In July 2016, NCI launched the largest study ever to investigate how genetic and biological factors contribute to breast cancer risk among Black women.[303] This collaborative initiative does not involve new patient enrollment but builds on years of research cooperation among investigators from many different institutions who will share biospecimens, data, and resources from 18 previous studies, resulting in a study population of 20,000 Black women with breast cancer. This work, in combination with previous efforts, should help advance our understanding of the social and biological causes that lead to disparities in cancer among underserved populations. A better understanding of the genetic contributions to differences in

[297] McKay JD, et al. *Nat Genet* 2017;49(7):1126-32. PMID: 28604730.
[298] Milne RL, et al. *Nat Genet* 2017;49(12):1767-78. PMID: 29058716.
[299] Michailidou K, et al. *Nature* 2017 Nov 2;551(7678):92-4. PMID: 29059683.
[300] Schumacher FR, et al. *Nat Genet* 2018;50(7):928-36. PMID: 29892016.
[301] Scelo G, et al. *Nat Commun* 2017;8:15724. PMID: 28598434.
[302] Machiela MJ, et al. *Nat Commun* 2018 Aug 9;9(1):3184. PMID: 30093639.
[303] https://www.cancer.gov/news-events/press-releases/2016/breast-cancer-genetics-black-women.

breast cancer diagnoses and outcomes among African Americans may lead to better treatments and better approaches for cancer prevention.

The RESPOND—or Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress—study is the largest coordinated research effort on biological and nonbiological factors associated with aggressive prostate cancer in African American men.[304] The study will investigate environmental and genetic factors related to aggressiveness of prostate cancer in African American men to better understand why they disproportionally experience aggressive disease compared with men of other racial and ethnic groups.

Environmental and Behavioral Risk Factors

Genetic changes that lead to cancer can arise from certain environmental exposures, including substances, such as chemicals in tobacco smoke, and radiation, such as ultraviolet rays from the sun. Behavioral and lifestyle factors—such as obesity, energy balance, and tobacco use—also play an important role. In addition to identifying cancer risk factors, research in this area provides data that regulatory agencies can use to set safety standards or reduce exposure to substances that are found to be associated with cancer.

In 2016, HHS released the *14th Report on Carcinogens,* which included 7 newly reviewed substances, bringing the cumulative total to 248 listings.[305,306] The Report on Carcinogens is a congressionally mandated report prepared for the HHS Secretary by the National Toxicology Program. The report identifies many different types of environmental factors, collectively called substances, including chemicals; infectious agents such as viruses; physical agents, such as X-rays and ultraviolet radiation; mixtures of chemicals; and exposure scenarios divided in two categories: known to be a human carcinogen or reasonably anticipated to be a human carcinogen.

The goal of the Report on Carcinogens is to safeguard the public by identifying substances in the environment that may affect human health. It is important to note that a listing in the report indicates a cancer hazard but does not by itself mean that a substance or a virus will cause cancer. For example, the National Toxicology Program tested exposure to radiofrequency radiation, such as used in 2G and 3G cell phones, for a link to disease. High exposure to radiofrequency radiation, meaning equal to or greater than the highest level allowed in cell phone emissions today, resulted in cancers in tissues surrounding nerves in the hearts of male rats, but not female rats nor any mice.[307,308] It is important to note that cell phones typically emit lower levels of radiofrequency radiation than the maximum level allowed and that these

[304] https://www.nih.gov/news-events/news-releases/nih-prostate-cancer-foundation-launch-large-study-aggressive-prostate-cancer-african-american-men.
[305] https://www.niehs.nih.gov/news/newsroom/releases/2016/november3/index.cfm.
[306] https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html.
[307] https://ntp.niehs.nih.gov/whatwestudy/topics/cellphones/index.html.
[308] https://www.niehs.nih.gov/news/newsroom/releases/2018/november1/index.cfm.

results in rodents cannot be compared directly to humans. The National Toxicology Program's conclusions were released as two technical reports, one for rat studies[309] and one for mouse studies.[310]

Radiation cannot be completely avoided, because natural sources are found in our environment in addition to our manufactured sources, such as cell phones and nuclear medicine. Five types or sources of ionizing radiation, which can induce chemical changes that affect cellular functions, are listed in the Report on Carcinogens as known to be human carcinogens, including X-rays and gamma rays. Substantial evidence links exposure to moderate or high doses of ionizing radiation, particularly in childhood, with increased risk of leukemia, but the association of leukemia with exposure to low-dose radiation is less certain. By analyzing historical cohort studies, researchers showed the risks of two types of leukemia (acute myeloid leukemia and acute lymphoblastic leukemia) were significantly increased in individuals exposed to low-dose ionizing radiation in childhood or adolescence.[311] These findings imply that the current system of radiological protection is prudent and not overly protective.

It is important to know which risk factors are behavioral and, thus, modifiable. The contributions of behaviors extend beyond the questions of whether and how these behaviors increase the risk of certain diseases to address how to help people modify these behaviors to reduce their risk and live healthier lives.

Certain infectious agents—including viruses, bacteria, and parasites—can cause cancer or increase the risk that cancer will form. Some viruses can disrupt signaling that normally keeps cell growth in check. For example, HPV infection is a known risk factor for cervical cancer. Infection with a specific type of HPV, HPV 16, causes about half of all cervical cancer cases each year. It is not known why HPV 16 is highly carcinogenic compared with other HPV types, nor why the majority of HPV 16 infections will clear on their own but a few will persist and lead to cervical precancer and cancer. Sequencing a large collection of samples from more than 5,000 HPV 16–infected women with and without cancer, researchers observed that a particular genetic sequence in a gene called *E7* is common to virtually all cervical cancers caused by HPV 16 worldwide.[312] This work further demonstrated that *E7* is the fundamental contributor to carcinogenesis—the process by which normal cells are transformed into cancer cells—in these cancer cases. This large genomic analysis presents a highly specific target for prevention and treatment of cervical cancer.

Moreover, researchers developed a new individual risk model for predicting which women who have HPV infection are at elevated risk for developing precancer or cancer lesions of the cervix or other genital areas.[313] This statistical model incorporates the duration of an individual's HPV infection—longer HPV

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[309] National Toxicology Program. *NTP Technical Report on the Toxicology and Carcinogenesis Studies in Hsd:Sprague Dawley Sd Rats Exposed to Whole-Body Radio Frequency Radiation at a Frequency (900 Mhz) and Modulations (Gsm And Cdma) Used by Cell Phones.* 2018. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr595_508.pdf.

[310] National Toxicology Program. *NTP Technical Report on the Toxicology and Carcinogenesis Studies in B6c3f1/N Mice Exposed to Whole-Body Radio Frequency Radiation at a Frequency (1,900 Mhz) and Modulations (Gsm and Cdma) Used by Cell Phones.* 2018. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr596_508.pdf.

[311] Little MP, et al. *Lancet Haematol* 2018;5(8):e346-58. PMID: 30026010.

[312] Mirabello L, et al. *Cell* 2017;170(6):1164-74. PMID: 28886384.

[313] Katki HA, et al. *J R Stat Soc Ser A Stat Soc* 2015;178(4):903-23. PMID: 26556961.

infection in an individual indicates a higher risk that it will cause precancer or cancer. The researchers observed that refining their model by incorporating more clinical history factors is necessary for precise risk predictions for individual patients.

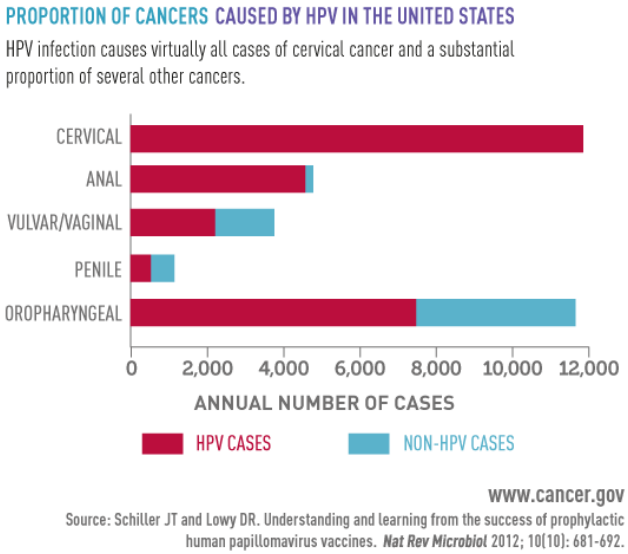

Figure 26. "Proportion of Cancers Caused by HPV in the United States": Infographic. Credit: NCI.

People who are obese may have an increased risk of several types of cancer. Conversely, eating a healthy diet, being physically active, and keeping a healthy weight may help reduce risk of some cancers. In the Nurses' Health Study II, a cohort study of female nurses aged 25–42 years, researchers found that female nurses classified as obese (body mass index [BMI] greater than or equal to 30) had a nearly doubled risk of early-onset colorectal cancer compared with female nurses who had a BMI of 18.5 to 22.9.[314] Specifically, women aged 20 to 49 who were considered overweight or obese based on BMI had up to twice the risk for colon cancer before age 50 compared with women with the lowest BMIs. These finding may shed light on previous studies that have shown increasing rates of colorectal cancer incidence and mortality among people younger than 50 years of age.

Tobacco use is a leading cause of cancer and of death from cancer. People who use tobacco products or who are regularly around environmental tobacco smoke (also called secondhand smoke) have an increased risk of cancer, because tobacco products and secondhand smoke have many chemicals that damage DNA. NCI's Tobacco Control Monograph series provides information about emerging public health issues in smoking and tobacco use control. Published in December 2016, Monograph 21, a collaboration between NCI and WHO, examined the current research and evidence base surrounding the economics of tobacco control—including tobacco use, tobacco growing, manufacturing and trade, tobacco product taxes and prices, and tobacco control policies and other interventions to reduce tobacco use and its consequences. Monograph 22, published in September 2017, examined tobacco-related health

[314] Liu PH, et al. *JAMA Oncol* 2019;5(1):37-44. PMID: 30326010.

disparities across the tobacco use continuum—initiation, secondhand smoke exposure, current use, frequency and intensity, cessation, relapse, morbidity, and mortality.[315]

Electronic cigarette (e-cigarette) use is rapidly increasing among adolescents in the U.S., with some suggesting that e-cigarettes are the cause of declining youth traditional (combustible) cigarette smoking. In an NCI-funded analysis of the self-reported smoking behaviors of thousands of schoolchildren nationwide, researchers found no evidence that the availability of e-cigarettes has served to accelerate the decline in youth smoking.[316,317] In fact, the researchers concluded the opposite: The popularity of e-cigarettes has led more children—not fewer—to become addicted to nicotine, which meets all criteria for being an addictive substance. Another study found that young adult (18–30 years old) e-cigarette use was associated with beginning traditional cigarette smoking within 18 months, supporting the need for policy and educational interventions designed to decrease use of e-cigarettes among nonsmokers.[318]

More than 10 million adults work the night shift, and many more are exposed to light at night, through outdoor and indoor lighting and electronic devices. Might these conditions cause cancer? The National Toxicology Program is undertaking a review to evaluate whether night shift work and light at night might be considered a human carcinogen. In 2016, the program gathered experts to discuss the current state of the field regarding health hazards associated with these conditions and to identify areas where further data or research are needed. This information may inform future research studies, health hazard assessments, and development of interventions to decrease adverse health outcomes.[319]

Focusing on Prevention

In 2019, more than 1.7 million people will be diagnosed with cancer in the U.S. In addition to the physical problems and emotional distress caused by cancer, the high costs of care are also a burden to patients, their families, and the public. Better cancer prevention will lead to a decrease in the number of new cases of cancer and the number of deaths due to cancer, and a reduction in the economic burden due to cancer. Studies that have more clearly defined how cancer develops and identified factors that can influence cancer risk are paving the way for important advances in cancer prevention.

One way to prevent cancers caused by viruses is to administer a vaccine against the viruses that are known risk factors, such as HPV and hepatitis B virus. Vaccines that protect against HPV can substantially reduce the risk of cervical cancer, and other cancers attributable to HPV infection. However, HPV vaccination rates are low, especially in countries with very high rates of cervical cancer and low resources. These vaccines are expensive, more than one dose is needed, and giving multiple doses can be difficult, especially in low resource settings. In FY 2018, NCI and the Bill & Melinda Gates Foundation funded a large study that will enroll 20,000 girls, ages 12 to 16 years, residing in Costa Rica to evaluate

[315] https://cancercontrol.cancer.gov/brp/tcrb/monographs/index.html.
[316] https://directorsblog.nih.gov/2017/01/.
[317] Dutra LM, Glantz SA. *Pediatrics* 2017;139(2). PMID: 28115540.
[318] Primack BA, et al. *Am J Med* 2018;131(4):443.e1-443.e9. PMID: 29242110.
[319] https://ntp.niehs.nih.gov/pubhealth/roc/listings/shiftwork/index.html.

whether a single dose of the HPV vaccine is just as effective as the recommended two doses.[320,321] This would reduce challenges to vaccine uptake in many parts of the world and improve cancer prevention through HPV vaccination.

The development of low-cost, second-generation HPV vaccines in LMICs and modification of existing vaccines, such as combinations with commonly administered vaccines, is limited. This is due to the lack of easily accessible, uniform, and standardized techniques, as well as the lack of processes and reagents for monitoring immune responses induced by licensed vaccines. The HPV Serology Standards Laboratory at the Frederick National Laboratory for Cancer Research launched an initiative in January 2017 co-funded by the Bill and Melinda Gates Foundation to address this challenge by standardizing and harmonizing serological assays for HPV antibody testing.[322] The standards, reagents, and assays will be made available to the scientific community, ensuring quality data from vaccine studies and enabling results to be compared across studies, which will facilitate vaccine development, implementation of new vaccine use recommendations, and identification of new vaccine candidates.

Recently, researchers developed a novel vaccine for the prevention of cancers driven by a specific genetic mutation. Up to 30 percent of human lung cancers are driven by mutations in a gene called *KRAS*. In 2017, NCI-funded and intramural researchers reported the development of an experimental vaccine that targets the KRAS protein with a specific mutation (*KRAS G12D*).[323] In experiments performed in mice, the vaccine reduced both the number and size of lung tumors that formed by more than 80 percent without adverse effects. Although preliminary, these findings suggest that a vaccine to prevent *KRAS G12D*-driven lung cancers or to prevent their recurrence may be feasible. The NCI PREVENT Cancer Preclinical Drug Development Program is currently supporting a study to evaluate its efficacy against other KRAS-driven cancer models, such as pancreatic cancer.[324]

Another way to prevent cancer is to block known pathways or interactions that can cause cancer to grow. The Prostate Cancer Prevention Trial involved 18,882 men from 1993 to 1997—making it one of the largest cancer prevention trials ever. Men were randomly assigned to finasteride (a drug used to treat symptoms of prostate enlargement, as well as male pattern baldness) or a placebo. The trial found that finasteride reduced prostate cancer risk by 25 percent.[325] Initial study findings suggested a possible link between use of the drug and a more lethal form of prostate cancer, but long-term follow-up shows that not to be true.[326]

To effectively prevent cancer, more is needed than new vaccines and drugs; scientific findings must be communicated in a way that is easy to understand to the public and patients. NCI and NIEHS co-fund the Breast Cancer and the Environment Communication Research Initiative, which supports research into the

[320] https://dceg.cancer.gov/research/cancer-types/cervix/escuddo.
[321] https://clinicaltrials.gov/ct2/show/NCT03180034.
[322] https://frederick.cancer.gov/science/laboratories/hpvserologylab.
[323] Pan J, et al. *Oncotarget* 2017;8(47):82689-99. PMID: 29137294.
[324] https://prevention.cancer.gov/major-programs/prevent-cancer-preclinical/supported-projects.
[325] Unger JM, et al. *J Natl Cancer Inst* 2016;108(12). PMID: 27565902.
[326] https://www.swog.org/news-events/news/2018/05/19/finasteride-safe-long-term-results-show.

process of effectively communicating scientific findings about breast cancer risk and the environment.[327,328] The initiative supports studies that focus on targeted risk communication regarding breast cancer and the environment and validation of the effectiveness of existing materials developed for patients and caregivers, health care professionals, advocates, and the general public.

Even with all that that is known about the risks associated with tobacco use, cigarette smoking remains the leading cause of preventable disease and death in the U.S. In January 2018, FDA, in partnership with NCI's *Smokefree.gov* team, launched *Every Try Counts* website.[329,330] This initiative is designed for adults who have attempted to quit in the past year, but were unsuccessful. This website provides evidence-based digital text messaging resources to encourage smokers to persevere as they try to quit smoking. In 2018, NCI also launched the Cancer Center Cessation Initiative as part of the Cancer Moonshot.[331] The initiative provides resources to NCI-Designated Cancer Centers to expand existing efforts intended to help their patients stop smoking. The long-term goal of this initiative is to help Cancer Centers build and implement sustainable tobacco cessation treatment programs to routinely address tobacco cessation with cancer patients.

Improving Screening, Detection, and Diagnosis

Checking for cancer (or for abnormal cells that may become cancer) in people who have no symptoms is called screening. Screening can help doctors find and treat several types of cancer early, before they cause symptoms. Early detection is important because abnormal tissue or cancer may be easier to treat when it is found early. By the time symptoms appear, cancer may have begun to spread and be harder to treat. Several screening tests have been shown to detect cancer early and to reduce the chance of dying from that cancer.

The cancer screening process includes steps for recruitment, screening, diagnosis, and referral for treatment. Multiple barriers exist that keep people from being screened, including fear of the procedure itself or preparation for the procedure, lack of access to care, and absent or inadequate doctor-patient discussions about screening. Based on this understanding, NCI has funded the Population-based Research to Optimize the Screening Process (PROSPR) network to better understand and improve the screening process in community health care settings. In April 2018, PROSPR funded one coordinating center and three research centers focused on cervical, colorectal, and lung cancer. Each research center includes at least three varied health care systems with diverse patient populations. The overall goal for PROSPR is to enhance understanding of the implementation and effects of screening as practiced in multiple health care environments in the U.S.[332] In addition to conducting research to evaluate factors that affect the

[327] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-017.html.
[328] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-15-015.html.
[329] https://smokefree.gov/everytrycounts/.
[330] https://www.fda.gov/tobaccoproducts/publichealtheducation/publiceducationcampaigns/everytrycountscampaign/default.htm.
[331] https://cancercontrol.cancer.gov/brp/tcrb/cessation-initiative.html.
[332] https://grants.nih.gov/grants/guide/rfa-files/rfa-ca-16-016.html.

quality of the screening process, the research centers will develop and pilot-test interventions aimed at improving the screening process for that cancer.

Research shows that individuals from medically underserved populations and racial and ethnic minority groups are more likely to be diagnosed with late-stage diseases that might have been treated more effectively or cured if diagnosed earlier. In the Kin Keeper[SM] Cancer Prevention Intervention study, researchers demonstrated that increased breast cancer literacy was associated with increased breast cancer screening rates among participants in a community-based health program.[333] In the program, community health workers gathered female family members in racial and ethnic minority groups—including Black, Latina, and Arabic—to learn about and share knowledge and experiences regarding breast and cervical cancers. The findings indicate that the higher the level of breast cancer literacy and the more motivated patients are, the more likely they are to be screened.

Increasing colorectal screening rates is one of the 10 recommendations of the Blue Ribbon Panel for the Cancer Moonshot and endorsed by the National Cancer Advisory Board. In response to these recommendations, NCI launched the national Screen to Save (S2S): NCI Colorectal Cancer Outreach and Screening Initiative to promote colorectal cancer awareness and screening among medically underserved populations, including racial and ethnic minorities and rural populations.[334] Through this initiative, community health educators will provide culturally tailored, evidence-based colorectal cancer information, education, and screening resources within communities nationwide. Initiated in nearly 40 geographically diverse locations in the U.S., more than 4,000 pre- and post-educational activity surveys have been collected and are under analysis.

Certain patterns of disease that are seen in members of a family—such as the types of cancer that develop, other noncancer conditions that are seen, and the ages at which cancer typically develops—may suggest the presence of an inherited susceptibility to cancer. Genes involved in many of the known inherited cancer susceptibility syndromes have been identified. Genetic testing can screen for and determine whether family members who have not (yet) developed a cancer have inherited the same variant as a family member who is known to carry a harmful (cancer susceptibility predisposing) variant.

For example, one inherited cancer predisposition syndrome is due to changes in a gene known as *DICER1,* which can lead to a variety of health outcomes, including increased risk for certain cancers and other conditions. In May 2016, the International Pleuropulmonary Blastoma Registry convened the inaugural International *DICER1* Symposium to develop consensus on genetic testing, surveillance (closely monitoring a patient's condition), and treatment recommendations.[335] The primary recommended approaches included individual and caregiver education and judicious imaging-based surveillance. As *DICER1* research expands, guidelines for screening, surveillance, and treatment will continue to be updated.

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[333] Talley CH, et al. *J Immigr Minor Health* 2017;19(6):1362-71. PMID: 26852236.
[334] https://www.cancer.gov/about-nci/organization/crchd/inp/screen-to-save.
[335] Schultz KAP, et al. *Clin Cancer Res* 2018;24(10):2251-61. PMID: 29343557.

NCI researchers recently demonstrated the feasibility of a new cancer screening protocol for patients with another rare inherited disorder, Li-Fraumeni syndrome.[336,337] This syndrome is caused by a genetic mutation in a gene called *TP53*. Many different cancers can develop due to this mutation; therefore, developing a universal surveillance approach has been difficult. Establishing an optimal surveillance protocol is important to reducing cancer and death in individuals with Li-Fraumeni syndrome. This study described the establishment and feasibility of an intensive cancer surveillance protocol for individuals with Li-Fraumeni syndrome, using such tools as whole-body, brain, and breast magnetic resonance imaging (MRI). Using this approach, prevalent cancers were detected at an early stage.

Studies performed during the last decade have strongly suggested that, in addition to benefits, screening has downsides—in particular, the risks of overdiagnosis (the diagnosis of cancers that would not threaten life or cause symptoms) and overtreatment (the treatment of cancers that would not threaten life or cause symptoms). For example, mammography is the most common tool used for breast cancer screening, but it is not known whether newer technologies are reducing a woman's risk of developing advanced cancer compared with older technology.

Recent research examined the relationship between breast cancer mass size, overdiagnosis, and the effectiveness of mammography screening. Researchers examined data on breast cancer in women aged 40 years and older from the SEER program from 1975 to 2012.[338] The researchers found that the introduction and increasing use of mammography for breast cancer screening resulted in the detection of a larger proportion of small breast tumors with a corresponding decrease in the proportion of tumors that were large; however, women were more likely to have their breast cancer overdiagnosed than to have early detection of a tumor that was destined to become large. The reduction in breast cancer mortality was predominantly due to improved systemic therapy and not to early detection.

In 2017, NCI launched the Tomosynthesis Mammographic Imaging Screening Trial (TMIST), the first large-scale breast cancer screening trial in nearly 25 years.[339] TMIST aims to compare two types of digital mammography approved by FDA: tomosynthesis (three dimensional or 3-D) and conventional (two dimensional or 2-D). Although 3-D mammography, the newer technology, is likely to detect more masses or cancers, it is also likely to lead to more procedures and treatments. Conducted through the NCI Community Oncology Research Program (NCORP), TMIST will involve up to 100 participating sites and enroll 165,000 asymptomatic women between the ages of 45 and 74 in the U.S. and Canada to compare the incidence of advanced breast cancers in those screened for 4 years with 3-D versus 2-D mammography.

Some cancer screening tests are invasive, can require extensive preparation by the patient, are expensive, and may lead to additional testing to confirm inconclusive findings. Advances in biomedical technologies, such as imaging and sequencing, are enabling the development of new tools for detecting and diagnosing

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[336] https://www.cancer.gov/news-events/press-releases/2017/li-fraumeni-syndrome-screening-study?cid=soc_tw_en_NCIMedia_press-release_screening_pt.
[337] Mai PL, et al. *JAMA Oncol* 2017;3(12):1640-5. PMID: 28772286.
[338] Welch HG, et al. *N Engl J Med* 2016;375(15):1438-47. PMID: 27732805.
[339] https://clinicaltrials.gov/ct2/show/NCT03233191.

cancer. Current research efforts will lead to more sensitive, less invasive, and more cost-effective cancer screening methods.

Current screening for Barrett's esophagus, a precancerous condition of the lower esophagus that increases the risk of esophageal cancer, requires endoscopy, an invasive and expensive procedure. A recent study described a simplified screening approach by identifying molecular patterns on DNA that are correlated with the presence of Barrett's esophagus.[340] Patients swallowed a pill-sized capsule attached to a thin silicone catheter. Once the capsule neared the stomach, a balloon with a textured surface was inflated and maneuvered to swab the lower esophagus, where Barrett's esophagus typically begins. The small dimensions of the balloon device allowed clinicians to retrieve samples quickly and easily without sedation. DNA from these samples can then be tested to determine risk.

Development of liquid biopsy technologies present a key research opportunity to discover approaches that are effective and noninvasive in detecting cancer early. These approaches aim to identify the presence of genetic material from cancer cells in the blood or molecular markers in urine or saliva that can identify precursor lesions or cancer at its earliest stages. The goal is to use these approaches to help detect, track, and treat cancer.

In current lung cancer screening approaches for high-risk individuals, such as smokers, if lesions or nodules are found on chest computed tomography (CT) scans, then invasive lung biopsies are needed to determine whether the lesions are cancerous. Recently, MagArray, funded by NCI's SBIR program, launched a commercial product called the REVEAL blood test for lung cancer risk assessment in smokers.[341] The REVEAL lung lesion characterization system helps clinicians assess lung nodules in current smokers and decide whether a costly and invasive biopsy is needed.

In 2018, a consortium of international and NCI-supported researchers reported the development of CancerSEEK, a blood test that measures the levels of 8 proteins and the presence of mutations in 16 cancer-associated genes to detect early-stage cancers in eight types of cancer (ovary, liver, stomach, pancreas, esophagus, colorectum, lung, and breast).[342–344] When this test was applied to previously collected blood samples from 1,005 patients with eight different types of cancer, the presence of cancer was correctly identified 70 percent of the time. Although promising, the sensitivity of detection is not yet high enough to be used for routine cancer screening, thus additional studies are underway.

The detection and analysis of cancer cell DNA in the blood is challenging because cancers may not shed a sufficient amount of DNA to be detected in blood samples, especially at early stages of disease. Investigators developed a novel sequencing method called targeted error-correction sequencing, which significantly increases the sensitivity of detecting mutations in 58 cancer-related genes in blood samples

[340] Moinova HR, et al. *Sci Transl Med* 2018;10(424). PMID: 29343623.
[341] https://www.prnewswire.com/news-releases/magarray-inc-announces-the-launch-of-the-reveal-blood-test-for-lung-cancer-risk-assessment-300691179.html.
[342] Cohen JD, et al. *Science* 2018;359(6378):926-30. PMID: 29348365.
[343] Kalinich M, Haber DA. *Science* 2018;359(6378):866-7. PMID: 29472467.
[344] Young RP, et al. *J Thorac Dis* 2018;10(Suppl 18):S2165-7. PMID: 30123550.

from early-stage cancer patients.[345,346] Using samples from patients with colorectal, breast, lung, or ovarian cancer, the technique identified cancer-related DNA mutations in 48 of 62 patients (77 percent) with advanced cancer (stages III and IV) and in 86 of 138 patients (62 percent) with early cancer (stages I and II). This result suggests that early detection of cancer by sequencing cancer cell DNA in the blood is a feasible approach but needs more refining.

Circulating cancer cell DNA is also being tested for early detection of residual disease in lung cancer—in other words, to detect lung cancer cells that remain after surgery or treatment. This study used a personalized and ultrasensitive approach to sequence circulating cancer cell DNA in patients with lung cancer.[347] Using this approach, the investigators identified a set of DNA mutations unique to an individual patient's cancer. The researchers monitored the patient both before and after treatment for circulating cancer cell DNA, searching for this set of DNA mutations in a blood sample. Results allowed the investigators to predict the recurrence, or return, of lung cancer with higher sensitivity than previous studies and to identify residual or recurrent disease earlier than standard-of-care imaging approaches.

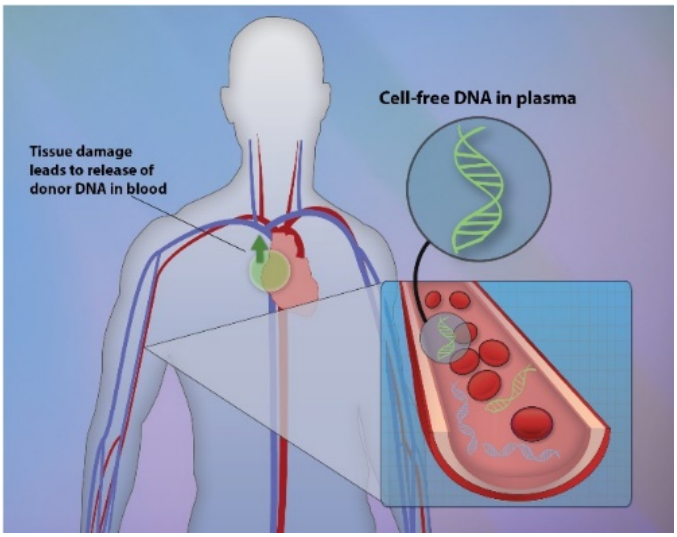

Figure 27. Scientists have discovered that dying tumor cells release small pieces of their DNA into the bloodstream. These pieces are called cell-free circulating tumor DNA (ctDNA). Credit: Jonathan Bailey, NHGRI.

People with HIV have a higher risk of developing B-cell lymphomas. Patients with lymphoma have been found to have a particular molecular marker in their blood, clonal immunoglobulin (Ig) DNA. The AIDS Malignancies Consortium conducted a pilot study to test whether high-throughput sequencing approaches could be used to detect clonal Ig in the blood of patients with HIV-associated lymphomas.[348] The study showed that identification and quantification of cancer-specific clonal Ig in the blood was possible in patients with HIV. These findings support the development of future studies into whether this

[345] https://www.nih.gov/news-events/nih-research-matters/detecting-early-signs-cancer-blood.
[346] Phallen J et al. *Sci Transl Med* 2017 Aug 16;9(403). PMID: 28814544.
[347] Chaudhuri AA, et al. *Cancer Discov* 2017;7(12):1394-1403. PMID: 28899864.
[348] Wagner-Johnston ND, et al. *Leuk Lymphoma* 2017;58(12):2939-42. PMID: 28508728.

molecular marker could be used to measure response to treatment and predict early relapse of lymphomas after treatment.

Technological advances in such areas as imaging are creating new avenues for advances in screening, early detection, and diagnosis. Research opportunities in imaging include the development of better tools for imaging cancers and for reading and interpreting imaging scans.

NCI-supported investigators designed the first total-body positron emission tomography (TB-PET) scanner to provide detailed information about tissues throughout the body.[349] Current PET scanners provide 3-D images but can image only small sections of the body in a procedure that can take 20 to 30 minutes and requires the use of a radioactive tracer. TB-PET is much more sensitive to the signal released by tracers, which means that the device can image the whole body in 30 seconds or less and also uses much less radioactivity than the standard PET scanner. This new technology will improve assessment of response to therapy in patients, aid in the development of new pharmaceuticals, and support new biological research, for example, by tracking cells in the body. This is a radical improvement for experimental medicine and diagnostic health care.

An NIH-supported biotech company, On Target Laboratories, is developing cancer-targeted fluorescent dyes to improve cancer surgery. One of its lead development candidates is OTL38, a near-infrared dye probe being evaluated for its ability to help surgeons locate and remove hard-to-find cancerous lesions that are often widespread. OTL38 has been proven safe and effective in a completed Phase II clinical trial for the treatment of ovarian cancer. In April 2018, it was announced that the first ovarian cancer patient was treated in a pivotal Phase III study that will assess the efficacy of OTL38 to identify additional ovarian cancer lesions not detectable by current approaches.[350]

The NIH Clinical Center released a large dataset of CT images to the public to help scientists develop more accurate detection of lesions or areas of abnormal tissue. These types of images are stored in hospitals' picture archiving and communication systems and are accompanied by vast amounts of clinical annotations, or measurements and markings recorded by radiologists as they interpret these images. Researchers at the Clinical Center used these annotations to develop the DeepLesion medical image database with 32,735 annotations from 4,427 unique patients.[351,352] This database includes radiology findings from across the body, such as lung nodules, liver cancers, and enlarged lymph nodes. One goal of the DeepLesion database is to develop a universal lesion detector, a computational method that can find all types of lesions with one unified framework.

[349] Cherry SR, et al. *Sci Transl Med* 2017;9(381). PMID: 28298419.
[350] https://www.prnewswire.com/news-releases/first-patient-treated-in-pivotal-phase-3-trial-to-evaluate-otl38-in-the-detection-of-ovarian-cancer-300624798.html.
[351] https://www.nih.gov/news-events/news-releases/nih-clinical-center-releases-dataset-32000-ct-images.
[352] Yan K, et al. *J Med Imaging* 2018;5(3):036501. PMID: 30035154.

Advancing Treatment

Research on the treatment of cancer is fundamental to improving outcomes for patients affected by these diseases. Efforts include the development of more effective and less toxic treatments, such as targeted therapies and immunotherapies, as well as the improvement of therapies that have existed for decades, such as chemotherapy and radiation therapy. Some studies focus on developing approaches to improve management of symptoms due to the side effects of treatments, while other studies test whether less intensive therapy or no therapy at all will result in the same outcome.

Radiation and Chemotherapy

Many research challenges remain in optimizing cancer treatment with conventional chemotherapy drugs and radiation therapy. Radiation therapy (also called radiotherapy) is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink the disease mass or tumor. Although radiation has been used for decades, further research is needed to refine the delivery of doses of radiation high enough to kill cancer cells while also sparing the surrounding normal tissues from harm.

Endometrial cancer, one of the most common gynecological cancer in the U.S., is typically diagnosed at an early stage and can be treated with surgery alone. In the early 2000s, clinical trials found that following surgery with radiation therapy reduced the rates of cancer recurrence, and this approach became the standard treatment for early-stage cancer patients. In a recent Gynecology Oncology Group trial, GOG-249, this method was confirmed to be more effective than an alternative treatment combining brachytherapy—a type of radiation therapy in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near cancer—with chemotherapy.[353] Survival was not improved and the risk of other adverse effects was greater when this alternative treatment was used, demonstrating that surgery followed by radiation therapy should remain the standard treatment for endometrial cancer.

For cancer patients with brain metastases, whole-brain radiation therapy after surgery is a standard medical treatment. This treatment can impair cognitive functions, such as memory, processing speed, and attention span. An alternative approach is stereotactic radiosurgery, in which high-dose radiation is specifically targeted to sites with lesions. A recent clinical study found that stereotactic radiosurgery had less risk of harming cognitive function compared to whole-brain radiation therapy and should be considered a standard treatment for patients with three or fewer brain metastases.[354]

Many cancer patients who undergo radiation therapy feel tired and rundown even after their treatments end. This fatigue can greatly interfere with patients' quality of life. Previous research suggests that inflammation from the radiation treatment causes fatigue to develop, but the mechanism of this fatigue and why fatigue can vary so much among patients remain unclear. A team of scientists analyzed the genomes of men with prostate cancer who were experiencing significant fatigue a year after radiation

[353] https://www.astro.org/uploadedFiles/_MAIN_SITE/News_and_Publications/News_and_Media_Center/News_Releases/2017/ASTRO17_Randall.pdf.
[354] Brown PD, et al. *Lancet Oncol* 2017;18(8):1049-60. PMID: 28687377.

treatment.[355] The study found that certain genes helped predict which patients were more likely to experience fatigue. Studies like this one could help find potential ways to treat cancer-related fatigue, or other adverse effects due to radiation therapy, based on people's genetic makeup.

Adrenal gland cancers occur in approximately 200 to 500 people in the U.S. annually. In 2018, FDA approved a new radioactive drug, iobenguane I-131, for the treatment of adults and adolescents age 12 and older with cancers of the adrenal gland.[356] The company that developed iobenguane I-131, Molecular Insight, received funding from the NCI SBIR program in 2005 to develop the agent.

Chemotherapy drugs act to stop or slow the growth of cancer cells but also can kill normal cells in the process. More research is needed to identify and develop new, more targeted chemotherapeutic agents, and to develop more effective treatments to alleviate the adverse effects of chemotherapy.

Kaposi sarcoma is a cancer that causes abnormal tissue to grow in the skin, the lining of the mouth and throat, lymph nodes, and the lungs and other internal organs. Kaposi sarcoma occurs most often in people with HIV whose immune systems have become weak and is particularly common in LMICs. In a clinical trial conducted by the AIDS Clinical Trial Group, the combination of antiretroviral therapy plus a specific chemotherapy, paclitaxel, led to slower progression rates and higher rates of progression-free survival than the other two chemotherapy regimens tested.[357,358] Paclitaxel plus antiretroviral therapy is a standard treatment in the U.S., where prevalence of Kaposi sarcoma has drastically fallen. Such studies are critical to improving AIDS survival rates and informing the knowledge base for HIV and cancer research.

Results from a groundbreaking NCI-sponsored clinical trial, called TAILORx, showed that most women with a common type of early-stage breast cancer do not benefit from chemotherapy given in addition to primary treatment.[359,360] TAILORx is the largest precision medicine trial completed to date and showed that up to 85 percent of patients had low or intermediate risk of cancer recurrence and that chemotherapy did not benefit the vast majority of these patients. The 15 percent of patients who had a high risk of recurrence did benefit from chemotherapy. These practice-changing results mean that the majority of women with early-stage breast cancer can be spared the short- and long-term effects of chemotherapy. One subset of younger women with an intermediate risk score seemed to benefit from chemotherapy; therefore, more research is needed to understand how to better identify and treat these patients.

Current methods to predict chemotherapy toxicity in patients with cancer are based on studies of younger adults, rather than older adults, and do not address variations in health status. A recent NIA-supported study validated the conventional prediction tool in a new group of patients aged 65 years or older across

[355] Feng LR, et al. *Transl Psychiatry* 2018;8(1):110. PMID: 29849049.
[356] https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm615155.htm.
[357] https://www.niaid.nih.gov/news-events/superior-aids-kaposi%E2%80%99s-sarcoma-treatment-identified.
[358] Hosseinipour MC, et al. *Clin Infect Dis* 2018;67(2):251-60. PMID: 29365083.
[359] https://www.cancer.gov/types/breast/research/tailorx.
[360] Sparano JA, et al. *N Engl J Med* 2018; 379(2):111-21. PMID: 29860917.

eight sites.[361] This study confirms that a tool incorporating geriatric assessment measures can reliably predict chemotherapy toxicity in older patients with cancer, which was not previously possible among older patients.

In addition, recent research demonstrated that diets that mimic fasting improve outcomes and reduce side effects in chemotherapy. NIA-supported investigators are studying fasting and fasting-mimicking diets as ways to prevent and treat cancer.[362,363] These studies will contribute to the identification of molecular targets for further drug development and novel dietary interventions to treat and prevent multiple diseases of aging by acting on the aging process and promoting multisystem rejuvenation.

Immunotherapy

Immunotherapy uses a variety of methods to stimulate or suppress the immune system to help the body fight cancer. Some types of immunotherapy target only certain cells of the immune system. Others broadly affect the entire immune system. Although recent advances in immunotherapy have shown positive results, this approach to treating cancer is still in its infancy. Many challenges remain, including how to optimize the immune response to eradicate cancer while avoiding runaway responses that cause autoimmune damage to normal tissues. An additional challenge is determining why current immunotherapies work in some patients or cancer sites but not in others.

In one type of immunotherapy known as adoptive cell transfer, cancer cells from a patient are sequenced to identify mutations, and the patient's lymphocytes (typically T cells) that recognize a subset of those mutations are then expanded in a laboratory and infused back into the patient to attack the cancer. For example, researchers in the NCI IRP demonstrated in separate case studies that a hormone receptor-positive, metastatic breast cancer[364,365] and a metastatic colorectal cancer with a mutant form of the *KRAS* gene[366] could be successfully treated with adoptive cellular transfer approaches using the patient's tumor-infiltrating lymphocytes. These case reports illustrate the power of immunotherapy and highlight the importance of additional studies to test its efficacy in other patients.

Similar to adoptive cell transfer, chimeric antigen receptor (CAR) T cell therapy involves sequencing cancer cells to identify mutations and then genetically engineering the patient's T cells to recognize and attack their cancer. Investigators in the NCI IRP pioneered the development of CAR T cell therapies. In 2017, FDA approved the first CAR T cell therapy to treat certain children and young adults who have B-cell acute lymphoblastic leukemia that does not respond to treatment or who go into remission and later relapse.[367]

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[361] Hurria A, et al. *J Clin Oncol* 2016;34(20):2366-71. PMID: 27185838.
[362] https://clinicaltrials.gov/ct2/show/NCT03340935.
[363] Nencioni A, et al. *Nat Rev Cancer* 2018;18(11):707-19. PMID: 30327499.
[364] https://www.cancer.gov/news-events/press-releases/2018/immunotherapy-targets-breast-cancer-case-report.
[365] Zacharakis N, et al. *Nat Med* 2018;24(6):724-30. PMID: 29867227.
[366] Tran E, et al. *N Engl J Med* 2016;375(23):2255-62. PMID: 27959684.
[367] https://www.cancer.gov/news-events/cancer-currents-blog/2017/tisagenlecleucel-fda-childhood-leukemia.

Another type of promising immunotherapy features immune checkpoint inhibitors. These antibodies target immune checkpoint proteins that act as brakes on the immune system. When these proteins are blocked, the brakes on the immune system are released and T cells are able to kill cancer cells better. Immune checkpoint inhibitor antibodies can target either the protein on the T cell (such as PD-1) or on the tumor cell surface (such as PD-L1).

In May 2017, FDA approved pembrolizumab, an anti-PD-1 inhibitor, for patients with late-stage solid cancers with a genetic feature known as high-microsatellite instability or mismatch repair deficiency.[368] This historic accomplishment was enabled by more than three decades of NCI-funded research in cancer genetics and immunology. In addition to hereditary and sporadic colorectal cancers, mismatch repair deficiency is associated with some cancers of the uterus, ovary, prostate, stomach, small intestine, biliary tract, and pancreas. This advancement is significant because targeting genetic characteristics, rather than where the cancer originates in the body, opens up new options for patients who might otherwise not be considered candidates for a drug.

Additionally, in 2017, FDA approved avelumab, an anti-PD-L1 inhibitor, for metastatic Merkel cell carcinoma—a rare, aggressive form of skin cancer—for adults and patients 12 years of age and older.[369] Avelumab is the first FDA-approved treatment for Merkel cell carcinoma. Trials based at NCI, whose infrastructure allows unparalleled, seamless collaboration between basic and clinical researchers, were instrumental in streamlining avelumab's approval.[370,371]

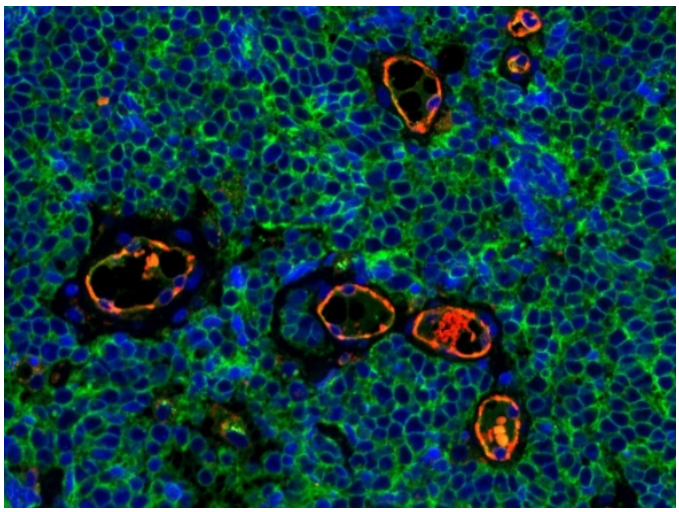

Figure 28. Immunofluorescent staining of Merkel cell carcinoma tumor tissue illustrating expression of CD200 (green) on the surface of tumor cells. CD200 plays a role in immunosuppression. The endothelial marker CD31 (red) highlights blood vessels. Credit: Isaac Brownell, NIAMS.

[368] Le DT, et al. *Science* 2017;357(6349):409-13. PMID: 28596308.
[369] https://ccr.cancer.gov/news/article/ccr-plays-key-role-in-first-FDA-approved-drug-for-treatment-of-merkel-cell-carcinoma.
[370] Kaufman HL, et al. *Lancet Oncol* 2016;17(10):1374-85. PMID: 27592805.
[371] Gulley JL, et al. *Lancet Oncol* 2017;18(5):599-610. PMID: 28373005.

Treatment with immune checkpoint inhibitors is effective for some patients with late-stage melanoma, but not all patients with melanoma respond to this treatment. Researchers in the NCI IRP and collaborative partners developed an immuno-predictive score (IMPRES) based on gene expression that can indicate whether melanoma in a specific patient is likely to respond to treatment with immune checkpoint inhibitors.[372,373] This predictor is an example of a tool that can guide treatment decisions to benefit patients.

Despite the improved overall survival of melanoma patients, melanoma brain metastasis is still associated with an extremely poor prognosis. A recent study compared the outcomes of melanoma patients with brain metastases treated with various types of drugs, surgery, and radiation.[374] Overall, survival from the time of the initial brain metastasis improved with the discovery of novel therapies. In particular, immune checkpoint inhibitor therapy with anti-PD-1 antibodies was found to significantly increase overall survival.

Mechanisms of response or resistance to immune checkpoint inhibitors are not well understood. An NCI-supported Lung Cancer Specialized Programs of Research Excellence (SPORE) research team identified a dormant, non-growing, population of T cells that is strongly associated with clinical benefit when PD-1 antibody is used to treat non-small cell lung cancer.[375] Additional studies will be required to determine whether this signature might be used as a clinical biomarker to predict response to immune checkpoint inhibitors.

In recent years, checkpoint inhibitors have led to remarkable success in treating patients with different cancers. However, mounting evidence shows that adverse rheumatologic effects, including inflammatory arthritis, can occur with the use of these drugs. For example, a case report published in 2016 documents rheumatologic disease in 13 cancer patients who were treated with the immunotherapy drugs ipilimumab or nivolumab from 2012 to 2016.[376] Clinicians should weigh the risk–benefit ratio when prescribing these drugs, and patients should watch for symptoms so they can see a rheumatologist early in an effort to prevent or minimize damage to the joints and other related organ systems.

More to that point, in March 2018, NCI, NIAID, and NIAMS convened a workshop titled *Cancer, Autoimmunity and Immunology*.[377] This workshop considered the occurrence of immune-related adverse events, or unexpected medical problems in the immune system that occur during treatment with a drug or other therapy. The workshop's goals were to (1) understand the biology of immune-related adverse events, which have occurred in cancer patients being treated with immunotherapies, and how that might inform the study of autoimmune disease and (2) define the potential for the study of autoimmune disease to lead to greater understanding of the treatment and management of immune-related adverse events during and following cancer therapies.

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[372] https://www.cancer.gov/news-events/press-releases/2018/melanoma-immunotherapy-predictor.
[373] Auslander N, et al. *Nat Med* 2018;24(10):1545-9. PMID: 30127394.
[374] Vosoughi E, et al. *BMC Cancer* 2018;18(1):490. PMID: 29703161.
[375] Gettinger SN, et al. *Nat Commun* 2018; 9(1):3196. PMID: 30097571.
[376] Cappelli LC, et al. *Ann Rheum Dis* 2017;76(1):43-50. PMID: 27307501.
[377] https://dctd.cancer.gov/NewsEvents/20180517_NCI_Convenes_Conference.htm.

Targeted Therapy

Advances in our understanding of cancer biology have created opportunities to develop targeted therapies—treatments that target specific changes in cancer cells, such as in genes and proteins, that underlie the development and progression of cancer. Many targeted therapies are small-molecule drugs or monoclonal antibodies, a type of protein made in the laboratory that can bind to substances in the body. Targeted therapies have expanded the treatment options available to patients with certain types of cancer and may have fewer side effects than other types of cancer treatment.

When a specific protein or class of proteins is known to be involved in the disease process, targeted therapies can be developed to inhibit or block the protein's function. For example, activation of the protein RAS in children and young adults with the genetic syndrome neurofibromatosis type 1 leads to non-cancerous tumor development. Selumetinib blocks the enzyme MEK to inhibit RAS activation, thus shrinking these tumors. Preliminary results from a Phase II trial confirm the results of a smaller trial in 2016 that demonstrated for the first time that selumetinib could shrink large tumors.[378,379] It also appeared to help improve other health problems associated with tumors caused by neurofibromatosis type 1. After a year of treatment, most patients in the trial reported improved pain scores, strength, and range of motion.

In addition, the RAS signaling pathway is activated in most low-grade gliomas. The Pediatric Brain Tumor Consortium conducted a Phase I clinical trial with selumetinib to identify a dose that is suitable for further testing in children.[380] Twenty percent of children treated with selumetinib showed sustained reductions in cancer volume, meeting criteria for partial response. Most of these children's cancers had gene changes that were thought to predict sensitivity to selumetinib. These positive results led to a follow-on Phase II study of selumetinib for children with low-grade glioma, and now a Phase III evaluation of selumetinib is in development by the Children's Oncology Group (COG).

Other clinical trials testing MEK inhibitors led to unexpected discoveries related to cancer cachexia, or the loss of body weight and muscle mass, and weakness that may occur in cancer patients. In biliary tract cancer patients, MEK inhibition effectively prevented muscle wasting even when cancers continued to grow.[381] Combining MEK inhibition with another targeted therapy, PI3K inhibition, led to both tumor loss and muscle preservation in colon cancer mouse models. Thus, combination targeted therapy might serve as a new approach for the treatment of cancer cachexia.

Developing targeted therapies requires the identification of good molecular targets—that is, targets that play a key role in cancer cell growth and survival—and the design and development of drugs that effectively hit, or bind to, those targets.

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[378] https://www.cancer.gov/news-events/cancer-currents-blog/2018/selumetinib-nf1-neurofibromas.
[379] Dombi E, et al. *N Engl J Med* 2016;375(26):2550-60. PMID: 28029918.
[380] Banerjee A, et al. *Neuro Oncol* 2017;19(8):1135-44. PMID: 28339824.
[381] Talbert EE, et al. *Mol Cancer Ther* 2017;16(2):344-56. PMID: 27811010.

For example, moxetumomab pasudotox binds a protein called the CD22 receptor on the surface of cancerous B cells and then is internalized and processed so that it releases its toxic payload to kill the cancer cells. In 2018, FDA approved moxetumomab for the treatment of patients with relapsed or refractory hairy cell leukemia.[382] This first treatment approved for this group of patients will allow hairy cell leukemia patients to avoid additional chemotherapy and has the potential to provide better long-term outcomes.

Non-small cell lung cancer accounts for 85 to 90 percent of lung cancers and is resistant to conventional chemotherapy, so patients with this type of lung cancer would benefit from more targeted therapies. An NCI-supported Lung Cancer SPORE research team identified a nuclear export receptor, *XPO1*, as an essential gene for survival in non-small cell lung cancer that has mutations in the *KRAS* oncogene family.[383] The results from this study provided supporting evidence for the initiation of an early-stage (Phase I/II) clinical trial in 2017, which is currently recruiting patients.[384]

Anaplastic large-cell lymphomas account for up to 15 percent of childhood lymphomas, and most of these cancers carry an anaplastic lymphoma kinase (*ALK)* gene fusion, a genomic alteration that can drive uncontrolled cell growth. Abnormalities in the *ALK* gene also occur in about half of inflammatory myofibroblastic tumors, a rare soft-tissue sarcoma. A recent study explored whether children with cancers that have alterations in the *ALK* gene may benefit from the targeted drug crizotinib, which blocks growth-promoting messages through the ALK signaling pathway. [385] The trial enrolled 26 children with anaplastic large-cell lymphoma or inflammatory myofibroblastic tumors. Cancers shrank in most of the children in the trial, and some of these responses have lasted for more than 2 years. The overall response rate for patients with anaplastic large-cell lymphoma was 90 percent; for patients with inflammatory myofibroblastic tumors, the response was 86 percent. Complete responses were seen in 80 percent of patients with anaplastic large-cell lymphoma but only in 36 percent of patients with inflammatory myofibroblastic tumors—highlighting the importance of having the right biomarker to select the patients who are most likely to benefit from a treatment.

Fusions involving tropomyosin receptor kinase genes (*TRK*) occur in a number of cancers in children and adults. One highly selective TRK inhibitor, larotrectinib, demonstrated marked and durable anticancer activity in patients with *TRK* fusion-positive cancers.[386] These responses occurred regardless of the patient's age or cancer type. FDA issued larotrectinib an orphan drug status and Priority Review, and subsequently, in November 2018, granted accelerated approval to larotrectinib. This is the second tissue-agnostic FDA approval for a cancer therapy. Larotrectinib builds on important basic science discoveries supported by NCI.

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[382] https://www.cancer.gov/news-events/cancer-currents-blog/2018/moxetumomab-fda-hairy-cell-leukemia.
[383] Kim J, et al. *Nature* 2016 538(7623):114-7. PMID: 27680702.
[384] https://clinicaltrials.gov/ct2/show/NCT03095612.
[385] Mossé YP, et al. *J Clin Oncol* 2017;35(28):3215-21. PMID: 28787259.
[386] Drilon A, et al. *N Engl J Med* 2018;378(8):731-9. PMID: 29466156.

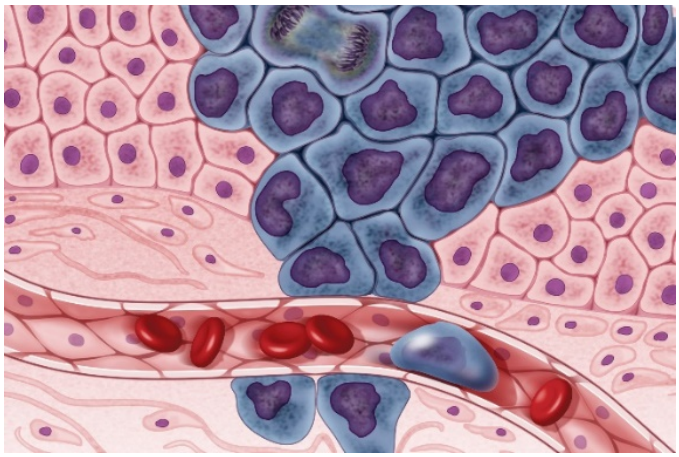

Figure 29. Diagram showing growing cancer cells (in purple) surrounded by healthy cells (in pink), illustrating a primary tumor spreading to other parts of the body through the circulatory system. Credit: Darryl Leja, NHGRI.

Metastatic disease, meaning cancer that has spread from the original site, is responsible for approximately 90 percent of cancer deaths. Researchers from NCATS and NCI worked with a multidisciplinary extramural team for 8 years to identify both a cellular target that is prevalent in metastatic cancer cells and a compound that inhibits the metastasis of cancer cells.[387–389] Metarrestin was found to selectively attack metastatic cancer cells in animal models of metastatic pancreatic, breast, and prostate cancers. In mice with pancreatic cancer that had spread to other organs, treatment with metarrestin shrank metastatic lesions and greatly extended how long the mice lived. Metarrestin appears to work by selectively killing cells that have developed a structure called the perinucleolar compartment within their nuclei—these structures develop almost exclusively in cancer cells and not in healthy cells. Currently, NCI is working with FDA to initiate human clinical trials in 2019. Therapy that can affect metastatic progression may improve outcomes for patients at all stages of disease.

The development of drugs that can target difficult-to-reach organs and tissues, such as the brain or central nervous system, requires novel approaches. For example, in 2017, the first drug using spherical nucleic acids was approved by FDA as an investigational new drug for an early-stage clinical trial (Phase 0) in glioblastoma multiforme.[390] Spherical nucleic acids have been used as gene regulation agents against several oncogene targets implicated in glioblastoma. This drug represents a revolutionary class of new drugs.

Drug resistance—either to traditional chemotherapy drugs or to newer targeted therapies—is another challenge in cancer treatment. More research is needed to uncover the mechanisms of drug resistance and identify ways to overcome it. Recently, researchers have taken mathematical modeling approaches to address the challenge of drug resistance. Standard-of-care cancer therapy most often is provided at

[387] https://ncats.nih.gov/bridgs/projects/active/pancreatic-cancer.
[388] Frankowski KJ, et al. *Sci Transl Med* 2018;10(441). PMID: 29769289.
[389] Vilimas T, et al. *Cancer Chemother Pharmacol* 2018;82(6):1067-80. PMID: 30306263.
[390] https://news.northwestern.edu/stories/2017/may/spherical-nucleic-acid-drug-human-brain-cancer-glioblastoma/.

the maximum tolerated dose for a patient. Utilization of mathematical modeling approaches to strategize both dose and timing of cancer therapy (known as adaptive therapy) is an active area of investigation in the NCI Physical Sciences-Oncology Network (PS-ON).[391] A PS-ON research team using evolutionary game theory computational models recently showed that advanced metastatic prostate cancer can be better controlled by using adaptive therapy to inform treatment cycles, suppress growth of cancer cells that are resistant to therapy, and lower cumulative drug dose for patients.[392]

Precision Medicine

Precision medicine is an approach that considers individual variability in genes, environment, and lifestyle for more targeted disease prevention and treatment for each person. This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It is in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals. Researchers at NIH hope to use an increased knowledge of the genetics and biology of cancer to find new, more precise treatments for various forms of this disease.

Launched in FY 2016, the NCI Molecular Analysis for Therapy of Choice (MATCH) trial is the largest precision medicine trial of its kind.[393] It is a Phase II trial open to patients for whom standard treatments failed or who have a rare cancer for which no standard treatment exists. Nearly 40 study arms are testing different therapies that target specific gene abnormalities in cancers. The original enrollment target of 6,000 patients was met nearly 2 years ahead of schedule, with many patients receiving screening through community hospitals. More than 1,100 institutions across the U.S. have enrolled patients for screening, representing all 50 states, the District of Columbia, and Puerto Rico. As of August 2018, 821 patients have been enrolled in a treatment arm. Almost half of the 39 treatment arms have already reached their enrollment goal of at least 35 patients. Currently, 18 arms are enrolling patients, and 4 new arms are in development. To date, four treatment arms have released preliminary findings. Among the first 6,000 patients enrolled for screening, more than 60 percent had cancers other than the four most common cancer types (i.e., breast, colorectal, non-small cell lung, and prostate cancers), providing more research opportunities for less common and rare cancers.

The NCI Pediatric MATCH trial, led by COG, opened in FY 2017 and is enrolling children with advanced solid cancers that have progressed or recurred on standard therapy.[394,395] As in the adult MATCH trial, genetic sequencing is being used to identify children and adolescents between the ages of 1 to 21 years whose cancers have a genetic abnormality for which either an approved or investigational targeted therapy exists. Patients with all types of solid cancers—including central nervous system cancers and non-Hodgkin's lymphomas, as well as histiocytic disorders (characterized by build-up of granulocytic immune

[391] https://physics.cancer.gov.
[392] Zhang J, et al. *Nat Commun* 2017;8(1):1816. PMID: 29180633.
[393] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.
[394] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match.
[395] https://clinicaltrials.gov/ct2/show/NCT03155620.

cells in the body)—are eligible for the trial. One unique aspect of the Pediatric MATCH trial is that germline DNA will be analyzed, so if a genetic abnormality is identified in the cancer, the treating physician will be informed whether the genetic abnormality is inherited or not and can provide additional recommendations regarding genetic testing and genetic counseling to the family. Currently, 10 treatment arms are open to accrual. As the trial continues, new treatment arms will open when drugs become available. Since the study opened, close to 400 children and adolescents have been enrolled for screening. The Pediatric MATCH trial is accessible at approximately 200 COG sites across the country, where the majority of pediatric cancer patients receive treatment.

Launched in 2016, the Applied Proteogenomics OrganizationaL Learning and Outcomes (APOLLO) Network is a tri-agency consortium among the DoD, VA, and NCI to use proteogenomics to better detect cancer and to apply targeted therapies based on the unique characteristics of each individual's cancer.[396,397] Proteogenomics is the study of how information about the DNA in a cell or organism relates to the proteins made by that cell or organism. The APOLLO Network brings together NCI with the nation's two largest health care systems, DoD and VA, to screen patients with lung cancer for genomic abnormalities and proteomic information that can be used to match their cancer types to targeted cancer therapies. The APOLLO network was inspired and developed through the Cancer Moonshot Initiative.

As part of NCI's Precision Medicine Initiative in Oncology, NCI and three European organizations (Cancer Research UK, Wellcome Sanger Institute, and Hubrecht Organoid Technology) have initiated the Human Cancer Model Initiative (HCMI), which aims to develop novel therapeutics and improve understanding of cancer etiology through the generation of novel cancer models that behave more like human cancers.[398,399] NCI's contributions include leveraging experience with other large-scale programs to ensure HCMI's success and providing funding and support to four Cancer Model Development Centers. HCMI-developed models, along with patient-associated clinical and molecular data, will be available to the research community as a resource in an effort to advance cancer and other research.[400]

Understanding Survivorship

Millions of adults and children in the U.S. are cancer survivors. An individual is considered a cancer survivor from the time of diagnosis through the balance of his or her life. NCI-supported studies have identified the long-term physical, psychological, and economic issues cancer survivors often face, so it is critically important to understand and develop interventions that address the unique health needs of this population. NIH research aims to improve both survivors' quality of life and their long-term survival.

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[396] https://proteomics.cancer.gov/news_and_announcements/applied-proteogenomics-organizational-learning-and-outcomes-apollo-network.
[397] https://proteomics.cancer.gov/programs/apollo-network.
[398] https://www.nih.gov/news-events/news-releases/international-collaboration-create-new-cancer-models-accelerate-research.
[399] https://ocg.cancer.gov/programs/HCMI.
[400] https://www.cancer.gov/about-nci/organization/ccg/blog/2016/human-cancer-models-initiative-launch.

Researchers are addressing survivorship issues by studying cancer and its burden on a population-wide scale. This includes identifying important trends or issues that affect cancer patients and survivors. An NCI study using SEER data and statistical modeling found that by 2040, there will be 26.1 million cancer survivors in the U.S., and 73 percent of them will be 65 or older. [401] Currently, 15.5 million survivors live in the U.S., 62 percent of whom are 65 or older. This steady and dramatic growth in the number of survivors will affect the health care system in a multitude of ways. These findings point to the need for health care providers to build collaborative care teams—including doctors, nurses, and other caregivers—to be able to respond to the complex needs of this vulnerable population. The study also notes the need to emphasize the benefits of lifestyle for cancer prevention and control across the life course.

Many studies have shown that cancer patients benefit from physical activity and that physical activity is important throughout the life course. However, being physically active can be difficult when dealing with adverse effects of treatment or disease. A study found a high degree of mobility disabilities in a sample of ovarian cancer survivors and identified associated symptoms, including abdominal bloating, fatigue, lack of appetite, numbness or tingling, and pain.[402] Symptom-related mobility disabilities (defined by self-reported difficulty walking) were identified in a majority (60 percent) of ovarian cancer patients and survivors. Research has shown that these symptoms can be mitigated through treatment and recovery processes. The identification of symptoms that are associated with impaired mobility among ovarian cancer patients and survivors is an important step in the development of effective symptom management strategies that can help patients and survivors improve their quality of life.

NIH also funds research to identify risk factors—related to treatment, lifestyle, and genetics—for the development of second primary cancers. Childhood cancer survivors, particularly those who received radiation to the chest as part of their treatment, are known to have an elevated risk of developing breast cancer later in life. Researchers conducted a GWAS of nearly 3,000 female survivors of childhood cancers to identify whether inherited genetic susceptibility may influence which survivors later develop breast cancer.[403] The team identified a common inherited genetic variant that showed increased breast cancer risk among patients treated with radiation to the chest. The study provides strong evidence that germline (or inherited) genetics can modify the effect of radiation exposure on breast cancer risk after childhood cancer.

Genetic counseling and genetic testing are recommended for women who have or may have a risk of developing hereditary breast or ovarian cancer. Studies that have demonstrated minimal psychological consequences for women receiving genetic counseling and genetic testing for hereditary breast or ovarian cancer have predominantly examined the experiences of White women. To address this gap, researchers followed up with a subset of participants from a population-based study of Black breast cancer survivors receiving genetic counseling and genetic testing for *BRCA1* and *BRCA2* gene mutations.[404] This study

[401] Bluethmann SM, et al. *Cancer Epidemiol Biomarkers Prev* 2016;25(7):1029-36. PMID: 27371756.
[402] Campbell G, et al. *Gynecol Oncol* 2016;143(3):578-83. PMID: 27653982.
[403] Morton LM, et al. *J Natl Cancer Inst* 2017;109(11). PMID: 29059430.
[404] Gonzalez BD, et al. *Psychooncology* 2018;27(12):2778-85. PMID: 30207419.

demonstrated minimal negative psychosocial outcomes following genetic counseling and genetic testing among young Black breast cancer survivors, irrespective of test results, confirming prior studies.

In February 2017, NCI launched the Detroit Research on Cancer Survivors (ROCS) study, the largest study to date of African American cancer survivors in the U.S.[405,406] This study leverages the Detroit area population-based cancer registry, which collects information about cancer incidence and survival and is part of the SEER program. Using these data, the study identified African Americans in Detroit who have recently been diagnosed with cancer. A unique aspect of this study is the inclusion of 2,780 family members to help researchers understand how a cancer diagnosis affects the mental, physical, and financial health of those providing care. The broad research agenda is to study major factors affecting cancer progression, recurrence, mortality, and quality of life among African American cancer survivors.

Facilitating Research

NIH supports important resources and services for cancer researchers. Providing and sharing large datasets accelerates discoveries in many research areas, including basic and population sciences. Similarly, providing access to key experimental resources and clinical trial infrastructure facilitates progress. Supporting collaborations across the federal government, with the private sector, and with the public generates new ideas, removes barriers that can stall projects, facilitates the dissemination of research results, and benefits patients.

NCI's SEER program sets national benchmarks for incidence and survival rates and is the primary source of data for reports on trends in cancer death rates.[407] The SEER program was established in 1973 in response to the *National Cancer Act of 1971*, which mandated that NCI collect, analyze, and disseminate all data useful in the prevention, diagnosis, and treatment of cancer. In FY 2018, NCI renewed contracts to the SEER program registries to expand the existing infrastructure to meet the research needs of the nation given evolving changes in cancer care.[408] The renewed program includes 16 registries covering 34 percent of the population. Infrastructure expansion includes real-time case eligibility assessment for cohorts, clinical trials, and other research studies, as well as the Virtual Linked Biorepository and the Virtual Pooled Registry. These expansions will create new research opportunities.

The Cancer Moonshot Initiative is an exceptional opportunity to accelerate progress in cancer prevention, diagnosis, treatment, and care.[409] The NCI National Cancer Advisory Board convened a Blue Ribbon Panel of top cancer experts to recommend areas poised to accelerate our understanding of cancer and bring benefit to patients. The Blue Ribbon Panel recommendations shape the ambitious scientific blueprint of the Cancer Moonshot, including vision, proposed scientific goals, and implementation. NCI has been

[405] https://www.cancer.gov/news-events/press-releases/2017/detroit-cancer-survivors-study.
[406] https://detroitrocs.org/dnn/.
[407] https://seer.cancer.gov/.
[408] https://grants.nih.gov/grants/guide/notice-files/NOT-CA-17-058.html.
[409] https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative.

engaged in Cancer Moonshot activities throughout FY 2016, 2017, and 2018 and has begun to implement all of the Blue Ribbon Panel recommendations.

Data sharing has been a primary goal of the Cancer Moonshot since its inception and requires new infrastructure to aggregate and harmonize cancer research data. In FY 2016, NCI launched the GDC and the NCI Cloud Pilots (now called the Cloud Resources).[410,411] The GDC provides the cancer research community a unified data repository that enables sharing of genomic and clinical data in support of precision medicine. The GDC centralizes, standardizes, and makes data accessible from large-scale NCI programs, such as TCGA and its pediatric equivalent, TARGET. As more researchers add clinical and genomic data to the GDC, it will become an even more powerful tool for making discoveries about the molecular basis of cancer that may lead to better care for patients. The GDC is a core component of both the Cancer Moonshot Initiative and the Precision Medicine Initiative-Oncology project.

In FY 2018, NCI embarked on building the Cancer Research Data Commons (CRDC), which includes the GDC and Cloud Resources as components.[412] The vision for the CRDC is a virtual, expandable computational infrastructure that provides secure access to many different data types across scientific domains, allowing users to store, analyze, and share results, and leveraging the storage and elastic computing power of the cloud. Overall, the technologies, standards, and processes established through the CRDC will contribute to the National Cancer Data Ecosystem recommended by the Cancer Moonshot Blue Ribbon Panel. The goal is to incorporate the spectrum of NCI cancer research data into the CRDC, allowing researchers to develop new knowledge that will expedite discovery and advance cancer care.

Advancing and optimizing collaboration is at the core of many of the Cancer Moonshot Blue Ribbon Panel recommendations. A number of research networks and consortiums were launched in FY 2017 and 2018, including the Drug Resistance and Sensitivity Network, Accelerating Colorectal Cancer Screening and Follow-up through Implementation Science, Human Tumor Atlas Network, Immuno-Oncology Translational Network, Pediatric Immunotherapy Discovery and Development Network, Fusion Oncoprotein in Childhood Cancers Consortium, Improving the Management of Symptoms During and Following Cancer Treatment Consortium, and Rare Tumor Patient Engagement Network. In FY 2017 and 2018 combined, NCI made more than 200 Cancer Moonshot awards (a combination of grants, administrative supplements, and contracts).[413]

[410] https://www.nih.gov/news-events/news-releases/newly-launched-genomic-data-commons-facilitate-data-clinical-information-sharing.
[411] https://gdc.cancer.gov/.
[412] https://datascience.cancer.gov/data-commons.
[413] https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative.

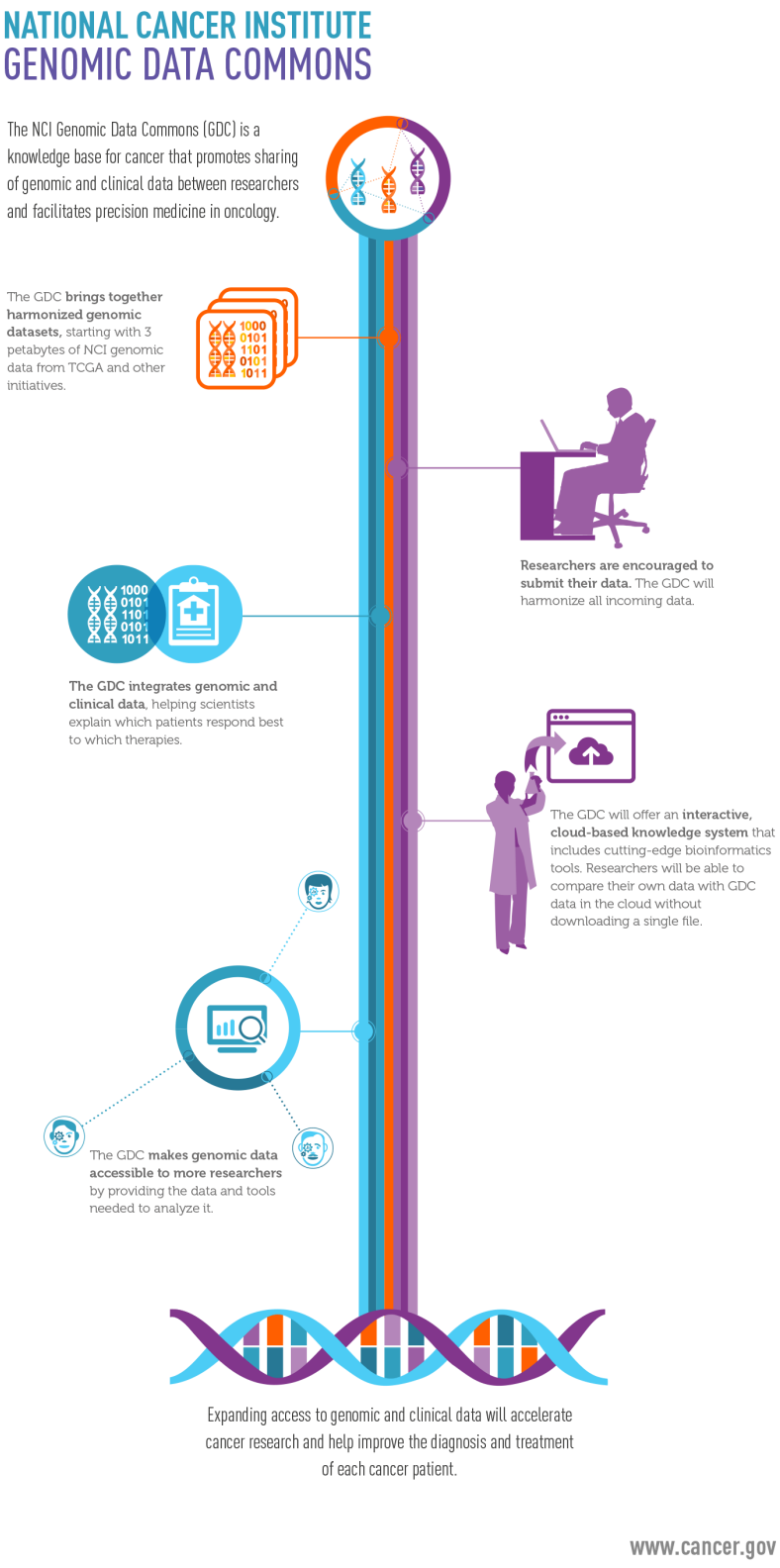

Figure 30. "National Cancer Institute Genomic Data Commons": Infographic. Credit: NIH.

In another effort to support the Cancer Moonshot, NCI launched a new drug formulary in a public–private partnership between NCI and pharmaceutical and biotechnology companies.[414,415] The NCI Formulary will enable investigators at NCI-Designated Cancer Centers to have quicker access to approved and investigational agents for use in preclinical studies and cancer clinical trials. This access will be particularly useful to investigators who would like to perform combination studies that focus on agents targeting molecular pathways from multiple collaborating pharmaceutical companies. The availability of agents through the NCI Formulary will expedite the start of clinical trials by alleviating the lengthy negotiation process—sometimes up to 18 months—that has been required for investigators to access such agents on their own. The NCI Formulary could ultimately translate into speeding the availability of more effective treatment options to patients with cancer.

NCI's National Clinical Trials Network (NCTN) has revolutionized clinical trials by providing funding and other support to cancer research organizations conducting cancer clinical trials. The NCI and VA Interagency Group to Accelerate Trials Enrollment (NAVIGATE) launched at 12 VA facilities across the country to enhance the ability of veterans to participate in trials carried out through NCI's NCTN and NCORP.[416] Through this interagency agreement, NCI will provide the infrastructure funding support needed for VA facilities to participate in NCI-sponsored trials, enhancing the ability of veterans with cancer to receive promising treatments locally. In turn, VA will manage organizational and operational activities within its national health care system to establish a network to focus on NCI trial goals.

Small businesses are a national resource for technological innovation and a mainstay of the economy. The SBIR and STTR programs were created by Congress to strengthen the role of small, innovative companies in federally supported research and development. In 2017, more than 90 clinical trials included NCI SBIR-funded technologies, such as Tocagen's Toca 511 retroviral replicating vector,[417,418] Epic Sciences' circulating tumor cell evaluation tools, and Bexion Pharmaceuticals' BXQ-350 nanovesicles to enter the brain and kill cancer cells.[419] Additionally, Oncoceutics expanded its Phase II clinical trial of the small molecule ONC-201 to include single-patient compassionate use in glioma patients with a specific genetic change, a missense histone H3 mutation.[420] Moreover, the NCI SBIR Development Center Workshop on Federal Resources for Accelerating Commercialization brought current NCI SBIR and STTR awardees together to learn how to use federal and local resources to advance commercialization. Representatives from federal agencies—including FDA, the Centers for Medicare & Medicaid Services (CMS), and the Biomedical Advanced Research and Development Authority (BARDA)—and experts from private organizations shared their expertise with attendees.

Finally, NCI recently launched a crowdsourcing website called the *Biomedical Citizen Science Hub*. Citizen Science is a collaborative approach to research involving the public, not just as subjects of the research or

[414] https://www.cancer.gov/news-events/press-releases/2017/nci-formulary-launch.
[415] https://nciformulary.cancer.gov/.
[416] https://www.cancer.gov/news-events/press-releases/2018/navigate-va-clinical-trials.
[417] https://clinicaltrials.gov/ct2/show/NCT01156584.
[418] https://clinicaltrials.gov/ct2/show/NCT02414165.
[419] https://clinicaltrials.gov/ct2/show/NCT02859857.
[420] https://clinicaltrials.gov/ct2/show/NCT03134131.

advisors to the research but as direct collaborators and partners in the research process itself. The Hub provides a free virtual collaboration space that offers anyone interested in biomedical, behavioral, and social citizen science and crowdsourcing the opportunity to connect, form groups, collaborate, find and share resources, develop tools, work on (and publish) papers, store databases, and more.

Neuroscience

Neurological disorders strike an estimated 100 million Americans each year, exacting an incalculable personal toll and an annual economic cost of hundreds of billions of dollars in medical expenses and lost productivity.[421] Given the important roles of the brain and nervous system in cognition, movement, behavior, and the body's physiological functions, the impacts of conditions affecting neurological function and mental health are wide ranging. Disorders of the brain and nervous system include developmental disorders, neuromuscular and movement disorders, mental health conditions, neurodegenerative diseases, brain and spinal cord injuries, headache and other pain disorders, autoimmune diseases and infections of the nervous system, brain tumors, and cerebrovascular diseases such as stroke and vascular dementia. These encompass both rare and common conditions arising from genetic and acquired causes and affecting people across all stages of life.

Summary of NIH Activities

Funding neuroscience research is central to the mission of several NIH ICs, including NIA, NICHD, NIDCD, NIMH, and NINDS. Although each NIH IC has a well-defined mission with respect to disease, several NIH components support complementary programs of basic neuroscience research that advance the missions of all. In addition, other ICs that fund neuroscience include NCCIH, NEI, NHLBI, NIAID, NIAMS, NIBIB, NIDA, NIEHS, and NINR. NIH spent $6.46 billion on neuroscience research in FY 2016, $7.32 billion in FY 2017, and $8.22 billion in FY 2018.[422]

Neuroscience at NIH had several overarching goals and initiatives for FY 2016–2018, including the BRAIN Initiative's work to support the development of new tools and technologies to revolutionize our understanding of the brain.[423–425] The NIH BRAIN Initiative is managed by the 10 ICs whose missions and current research portfolios align with the goals of the initiative: NCCAM, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIMH, and NINDS. Launched in 2013 and passing its fifth year, the BRAIN Initiative continues to support groundbreaking scientific projects. Many of the accomplishments mentioned throughout this section on neuroscience research were funded, either in part or completely, through the BRAIN Initiative. Through 2018, NIH has funded more than 500 investigators with a cumulative total investment of nearly

[421] Gooch CL, et al. *Ann Neurol* 2017;81(4):479-84. PMID: 28198092.
[422] https://report.nih.gov/categorical_spending.aspx.
[423] https://www.braininitiative.nih.gov.
[424] https://www.nimh.nih.gov/news/science-news/2017/nih-brain-initiative-launches-cell-census.shtml.
[425] Koroshetz W, et al., *J Neurosci* 2018;38(29):6427-38. PMID: 29921715.

$1 billion.[426] These awards support projects by individual laboratories and cross-disciplinary, team-based science, and cutting-edge technology development. To date, hundreds of publications have described new BRAIN-related advances and techniques for studying the brain in action. In FY 2017, NIH began funding neuroethics research as part of the BRAIN Initiative, and the BRAIN Initiative's Neuroethics Division has already hosted workshops focusing on a variety of topics, including ethical foundations of novel neural technologies; issues around stem cells, neural organoids, and ex vivo human brain tissue; development of ethical guidelines for neurotechnologies; and ethical issues in research with neural devices. In April 2018, NIH invited an external group of experts to advise NIH on how best to design the second half of the Initiative's lifespan, dubbed BRAIN 2.0. NIH leadership also held a series of public, cross-country workshops and events on BRAIN 2.0 to solicit input and expert consultations from leaders in the field, as well as hear from stakeholders in the scientific community and the public.

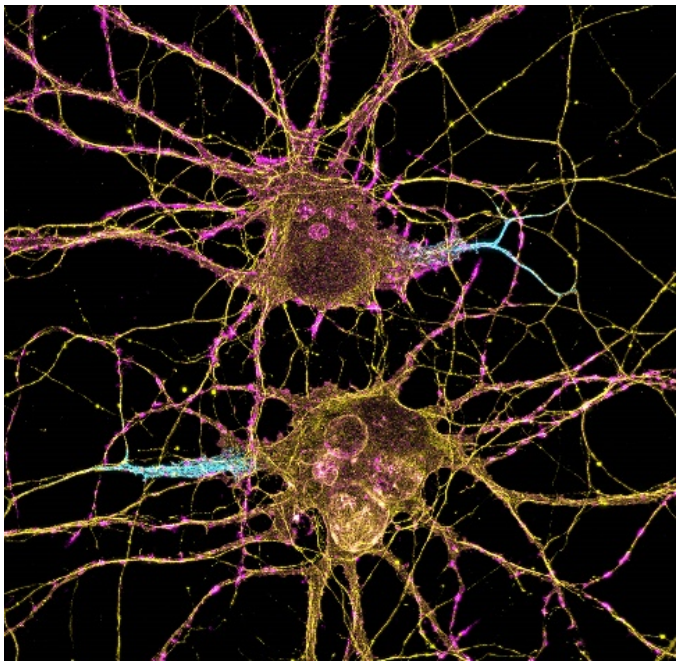

Figure 31. Image of neurons. Scientists have been developing astounding new tools for exploring neural circuits that underlie brain function throughout the first 5 years of NIH's Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative. Credit: NeuroCyto Lab, INP, Marseille, France.

Other key initiatives include the NIH HEAL Initiative to provide scientific solutions to the opioid crisis by improving pain care and improving treatment for opioid misuse and addition, and offering hope for individuals, families, and communities affected by this devastating crisis[427]; the Autism Centers of Excellence (ACEs) to support large-scale multidisciplinary studies on autism spectrum disorders (ASDs), with the goal of determining the disorders' causes and best treatments (see Chapter 4 for a full update

[426] https://www.braininitiative.nih.gov/.
[427] https://www.ninds.nih.gov/News-Events/Directors-Messages/All-Directors-Messages/NIH-HEAL-initiative.

on the ACEs).[428–430] In addition, NIA, in collaboration with NINDS, is enabling some of the nation's leading scientists to tackle the problem of Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) at an unprecedented scale and pace.[431–434] Several neuroscience advances are discussed in the subsections below, and additional examples can be found throughout other sections of Chapter 3.

Understanding the Biology of the Brain and Brain Disorders

Basic research is essential for long-term progress against neurological diseases—it seeks to understand how the nervous system develops and functions, as well as what goes wrong in disease. Maintaining this breadth of basic research is essential to the NIH mission.

The Developing Brain

NIH supports research on how the brain forms, grows, and changes. Studying the nervous system advances understanding of our basic biology and body function. Knowing how things typically work can help shed light on what may happen when there are problems. The nervous system not only works to produce thoughts, emotions, and behavior, but also controls important body functions, like breathing. Some key areas of research include typical and atypical nervous system development in model organisms and in humans; genetic disorders; and intellectual and developmental disabilities, including learning disabilities. Additional developmental research is included in the Life Stages, Human Development, and Rehabilitation Section of this chapter.

Viruses, like Zika virus, can be transmitted from an infected pregnant woman to her baby during pregnancy and can result in serious birth defects, including microcephaly. Using neural progenitor cells produced from human-induced pluripotent stem cells (iPSCs), NIH-funded researchers showed that Zika virus can infect and kill the neural progenitor cells that give rise to the cerebral cortex.[435] They also showed that the virus exploits the cell's own machinery to produce and release more Zika virus to infect more cells. The same group published a follow-up study in which they showed that Zika virus can infect brain-region-specific organoids generated from human iPSCs, and Zika virus infection causes a decrease of neuronal cell-layer volume resembling microcephaly.[436] In a collaboration with NCATS, they used these technologies and insights to demonstrate a promising strategy for screening drugs that either inhibit Zika virus infection or protect brain cells.[437]

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[428] https://www.nichd.nih.gov/research/supported/ace.
[429] https://grants.nih.gov/grants/guide/rfa-files/rfa-hd-17-008.html.
[430] https://grants.nih.gov/grants/guide/rfa-files/rfa-hd-17-009.html.
[431] https://model-ad.org/.
[432] https://www.nia.nih.gov/research/abc-ds.
[433] https://www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc.
[434] https://www.nih.gov/file/27681.
[435] Tang H, et al. *Cell Stem Cell* 2016;18(5):587-90. PMID: 26952870.
[436] Qian X, et al. *Cell* 2016;165(5):1238-54. PMID: 27118425.
[437] Xu M, et al. *Nat Med* 2016; 22(10):1101-7. PMID: 27571349.

Intellectual and developmental disabilities are disorders that are usually present at birth and that negatively affect the trajectory of the individual's physical, intellectual, and/or emotional development. Intellectual and developmental disabilities can be caused or influenced by a variety of genetic and environmental factors, including gene mutations, health behaviors, complications during pregnancy or birth, and the exposure of the pregnant mother or child to infections or environmental toxins. The causes of some intellectual and developmental disabilities, for example Fragile X syndrome and Down syndrome, are well understood.

Fragile X syndrome is the most common genetic form of intellectual disability in males. Individuals with Fragile X syndrome have an *FMR1* gene that is silenced or turned off; this stops the gene from producing the FMRP protein, which is necessary for normal brain development. Various tools have been used to try to turn the *FMR1* gene back on or assess how much of the *FMR1* gene must be expressed to achieve normal brain development and function. Researchers supported by NICHD and NINDS found that removing methyl groups from DNA repeats in the *FMR1* gene turned the *FMR1* gene back on, leading to production of FMRP protein.[438] These results suggest that demethylation of DNA could form a basis for future therapeutic interventions for people with Fragile X syndrome.

To measure how much the *FMR1* gene is expressed, researchers used the gene-editing method CRISPR/Cas9 to insert a gene called Nano luciferase (*Nluc*) and link it to the *FMR1* gene on the X chromosome of neural stem cells derived from Fragile X syndrome patients.[439] Molecules that reactivated expression of the silenced *FMR1* gene turned on the *Nluc* gene, producing a protein that glows when exposed to a specific chemical. This method enabled researchers to quickly test the efficacy of many different molecules in reactivating the *FMR1* gene, which could provide the basis for screening novel treatments for Fragile X syndrome.

In addition, the Centers for Collaborative Research in Fragile X support research to improve the diagnosis and treatment of Fragile X syndrome by stimulating multidisciplinary and multi-institutional research.[440] In 2018, a brain imaging study of infants with Fragile X syndrome showed that 12 of 19 major white-matter connections were significantly underdeveloped in children with Fragile X syndrome, compared with typically developing children.[441] These changes were established by 6 months of age, far younger than the average age at which Fragile X syndrome is diagnosed, and did not worsen over time. In 2017, NIH embarked on a process, led by NICHD, to develop a new NIH Strategic Plan for Research on *FMR1*-Associated Conditions.

NICHD partners with other ICs to support a wide range of research, including understanding Down syndrome throughout the life span to clarify how genetics affects cognitive function,[442] characterize how

[438] Liu XS, et al. *Cell* 2016;172(5):979-92.e6. PMID: 29456084.
[439] Li M, et al. *Stem Cells* 2017;35(1):158-69. PMID: 27422057.
[440] https://www.nichd.nih.gov/research/supported/ccrfx.
[441] Swanson MR, et al. *JAMA Psychiatry* 2018;75(5):505-13. PMID: 29617515.
[442] https://projectreporter.nih.gov/project_info_description.cfm?aid=8858654&icde=42704980.

development is affected,[443] develop outcome measures for assessing therapies and behaviors,[444] identify potential factors that could be used to predict cognitive decline with age,[445] understand the link between Down syndrome and Alzheimer's disease,[446] and promote interdisciplinary studies that contribute further to our knowledge of the cognitive and behavioral manifestations of intellectual and developmental disabilities.

Down syndrome is the most common genetic cause of an intellectual and developmental disability, affecting 1 in 700 babies. Researchers supported by NICHD did genome-wide analysis comparing gene expression in brains of deceased individuals with Down syndrome with brains of individuals without Down syndrome.[447] Although an extra copy of chromosome 21 is the underlying genetic defect in Down syndrome, they found differences in the expression of more than 1,400 genes across all of the chromosomes. Notably, genes that had significantly lower expression in Down syndrome were involved in the maturation and viability of oligodendrocytes, the special brain cells that form myelin, a substance vital to brain function because it insulates and protects nerve cells, speeding up the transmission of signals and communication between nerve cells.

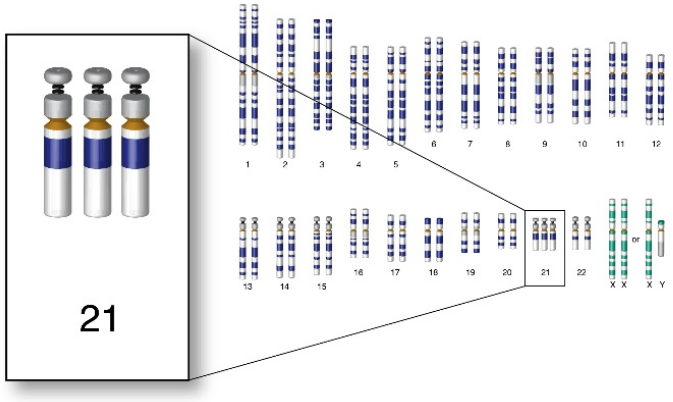

Figure 32. Down syndrome is a genetic disease resulting from a chromosomal abnormality. An individual with Down syndrome inherits all or part of an extra copy of chromosome 21. Credit: Darryl Leja, NHGRI.

INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) is an NIH-wide initiative involving 18 ICs that aims to understand critical health and quality-of-life needs for individuals with Down syndrome.[448] INCLUDE will investigate conditions that affect individuals with Down syndrome and the general population, such as AD/ADRD, autism, cataracts, celiac disease, congenital heart disease, and diabetes. INCLUDE aims to conduct targeted, high-risk, high-reward basic science studies on chromosome 21; assemble a large study population of individuals with Down syndrome; and include individuals with Down syndrome in new and existing clinical trials.

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[443] https://projectreporter.nih.gov/project_info_description.cfm?aid=9263673&icde=42704980.
[444] https://projectreporter.nih.gov/project_info_description.cfm?aid=9543031&icde=42704980.
[445] https://projectreporter.nih.gov/project_info_description.cfm?aid=9417955&icde=42704980.
[446] https://projectreporter.nih.gov/project_info_description.cfm?aid=9564690&icde=42704980.
[447] Olmos-Serrano JL, et al., *Neuron* 2016;89(6):1208-22. PMID: 26924435.
[448] https://www.nih.gov/include-project.

Although the causes of Fragile X syndrome and Down syndrome are well understood, the underlying causes of many other intellectual and developmental disabilities, for example ASD, are often unclear and may vary substantially across individuals. The NICHD's Learning Disabilities Research Centers (LDRC) Consortium was established to develop knowledge on the causes, origins, and developmental course of learning disabilities.[449] The LDRC Consortium addresses learning disabilities that affect reading and writing, including basic reading skills, reading fluency, reading comprehension, and written expression. Complementing the LDRC Consortium, the Learning Disabilities Innovation Hubs focus on understudied research topics and on projects that study people diagnosed with and at risk for learning disabilities.[450] Projects also include mentorship of researchers who are in the early stages of their careers, with a focus on enhancing involvement of underrepresented groups in scientific careers.

The Functioning Brain

NIH has a key role in supporting basic research to understand how the nervous system operates and what goes wrong in disease. Neuroscientists study nervous system function and dysfunction on many different levels. They examine molecules, nerve cells, nerve networks, and brain structure, individually and collectively, and how these components interact to perform different activities.

Around 80 percent of human protein-encoding genes are expressed in the brain.[451] These genes influence the development and function of the brain and, ultimately, control how we move, think, feel, and behave. Researchers in the NIH Common Fund's Epigenomics program used a new neuroimaging tool to show, for the first time, patterns of where genes are being turned off or on in living human brains.[452–455] They observed similar patterns within and between individuals. This research lays the groundwork for understanding epigenetic dynamics in the human central nervous system and how they change in such diseases as schizophrenia and Alzheimer's disease.

Each cell turns on only a fraction of its genes, while it silences the rest. For example, genes that are expressed in brain cells may be silenced in liver cells or heart cells. Some genes are turned on only during the early months of human development and then are silenced later. Researchers in the NIH Common Fund's 4D Nucleome program have discovered that unstable repeated DNA sequences associated with neurodegenerative diseases are nearly all located at boundaries between discrete 3-D regions of the genome in the nucleus.[456,457] Using the gene *FMR1* associated with Fragile X syndrome as a model, they found that misfolding in the repeated DNA region disrupted the boundary between these domains and

[449] https://www.nichd.nih.gov/research/supported/Pages/ldrc.aspx.
[450] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-17-003.html.
[451] Hawrylycz MJ, et al. *Nature* 2012;489(7416):391-9. PMID: 22996553.
[452] https://www.pbs.org/newshour/science/new-technique-sees-brain-gene-activity-living-color.
[453] https://www.scientificamerican.com/article/new-imaging-technique-provides-first-look-at-gene-activity-in-the-living-human-brain/.
[454] https://commonfund.nih.gov/epigenomics.
[455] Wey HY, et al. *Sci Trans Med* 2016;8(351):351ra106. PMID: 27510902.
[456] https://scienmag.com/penn-researchers-class-of-neurological-disorders-share-3d-genome-folding-pattern/.
[457] https://commonfund.nih.gov/4Dnucleome.

led to the gene's being turned off.[458] This research suggests that understanding the link between DNA repeat instability and genome folding could lead to novel therapeutic options.

Scientists do not yet fully understand what causes Alzheimer's disease in most people. In people with early-onset Alzheimer's disease, a genetic mutation may be the cause. Late-onset Alzheimer's disease arises from a complex series of brain changes that occur over decades. The causes probably include a combination of genetic, environmental, and lifestyle factors. The importance of any one of these factors in increasing or decreasing the risk of developing Alzheimer's disease may differ from person to person.

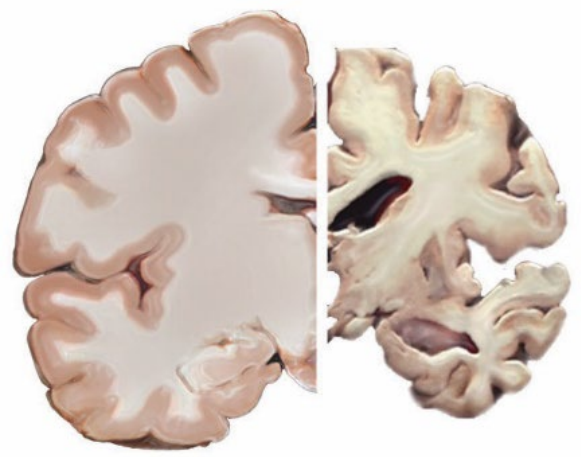

Figure 33. Comparison of a healthy brain (left) and a brain with severe Alzheimer's disease (right). Credit: NIA.

Analysis of large datasets from post-mortem brain samples of people with and without Alzheimer's disease has revealed new evidence that viral species, particularly herpesviruses, may have a role in Alzheimer's disease biology.[459] NIA-supported investigators harnessed data from brain banks and cohort studies participating in the Accelerating Medicines Partnership Alzheimer's Disease (AMP-AD) project. The authors emphasize that their findings do not prove that the viruses cause the onset or progression of Alzheimer's disease. Rather, the findings show that viral DNA sequences and activation of biological networks—the interrelated systems of DNA, RNA, proteins, and metabolites—may interact with molecular, genetic, and clinical aspects of Alzheimer's disease.

This article has stimulated an enhanced collaboration with the NIH OAR—OAR and NIA believe that it is critical to understand the neurodegenerative processes contributing to central nervous system impairment in older adults, especially adults living with HIV. For example, in 2018, OAR announced funding for cross-disciplinary research that will help to understand the similarities and differences between the mental and physical declines observed in Alzheimer's disease and HIV-associated neurocognitive disorder (HAND).[460] Some projects will explore how the mental and physical declines interact to increase disease burden and cognitive impairment. Others will look at how Alzheimer's disease–related conditions may

[458] Sun JH, et al. *Cell* 2018;175(1):224-38.e15. PMID: 30173918.
[459] Readhead B, et al. *Neuron* 2018;99(1):64-82.e7. PMID: 29937276.
[460] https://www.oar.nih.gov/trans-nih-hiv-research-program/project-spotlight/national-institute-on-aging-collaboration.

cause HAND in older adults living with HIV. The awards include annual workshops that will focus on assessing the initiative's progress and contribute to the development of a core of researchers from different disciplines.

In addition to genetics, cell types and cell signaling pathways contribute to Alzheimer's disease progression. For the first time, NIA IRP investigators showed that astrocyte-derived exosomes, small particles shed by all cells, can be isolated from plasma and that they contain complement proteins.[461] The research team showed that Alzheimer's disease patients have higher levels of complement proteins in their astrocyte-derived exosomes than age-matched controls without cognitive problems, suggesting that these astrocyte-derived exosomes are potentially toxic to nearby neurons.

Although Alzheimer's disease is the most common cause of dementia among older adults, it is only one type in a related family of dementias, including Lewy body dementia. The purpose of the Lewy Body Dementia Center Without Walls (CWOW) program is ultimately to understand how toxic species of alpha-synuclein and amyloid-beta—proteins found in the brain—produce the clinical pathology characteristic of Lewy body dementia.[462] This FOA by NINDS and NIA invites applications that will systematically and comprehensively characterize alpha-synuclein and amyloid-beta subspecies present in human Lewy body dementia post-mortem brain tissue, identify toxic subspecies and potential mechanisms of toxicity, and characterize any interactions between the proteins that may contribute to increased toxicity or explain selective vulnerabilities of nerve cells and circuits.

The signature pathology in Parkinson's disease is Lewy bodies, which have been found to be composed of a protein called synuclein. Parkinson's disease, Lewy body disease, and multiple system atrophy are considered synucleinopathies. Scientists are trying to better understand the normal and abnormal functions of alpha-synuclein and its relationship to genetic mutations that impact Parkinson's disease and Lewy body dementia. Researchers showed that normal LRRK2 kinase activity was selectively enhanced in dopamine neurons in post-mortem brain tissue from patients with Parkinson's disease and in two different rodent models—a genetic and an environmental model of Parkinson's disease.[463] These findings suggest that both genetic and environmental causes of Parkinson's disease can be linked to the activity of LRRK2 protein and that the drugs being developed for patients with the LRRK2 mutation could benefit a much greater number of people with the disease than previously thought.

In addition, previously identified Parkinson's disease–causing gene mutations suggest that both mitochondrial (energy-producing) and lysosomal (protein-degradation) mechanisms contribute to the disease. However, it has been unclear how disruption of these two distinct pathways results in indistinguishable clinical and pathological phenotypes. Using dopamine neurons derived from patients with either sporadic or familial Parkinson's disease, researchers discovered that oxidation of dopamine links mitochondrial stress, lysosomal dysfunction, and alpha-synuclein accumulation.[464] Importantly, they also showed that these effects are seen in human cells and not mouse models because mice have lower

[461] Goetzl EJ, et al. *Ann Neurol* 2018;83(3):544-52. PMID: 29406582.
[462] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-18-024.html.
[463] Di Maio R, et al. *Sci Transl Med* 2018;10(451). pii: eaar5429. PMID: 30045977.
[464] Burbulla LF, et al. *Science* 2017;357(6357):1255-61. PMID: 28882997.

levels of dopamine. These studies identified a common mechanism that applies to Parkinson's disease caused by different gene mutations, suggesting a point of intervention in prevention and therapy development.

Parkinson's disease destroys dopamine-producing cells in the brain region the substantia nigra within the basal ganglia, which connects to adjacent brain areas and affects functions other than motor control, including learning, drug addiction, and emotions. The main therapy for Parkinson's disease is levodopa, also called L-dopa. Nerve cells use levodopa to make dopamine to replenish the brain's dwindling supply. Maintaining dopamine levels requires an elegant balance, because psychosis is also associated with dopamine system dysfunction, characterized by greater dopamine release and synthesis capacity in the striatum.

Understanding impaired cognition and the underlying neural circuits is a key priority for NIMH in its mission to understand serious mental illnesses.[465] In a collaborative effort among NIMH-supported extramural and IRP researchers, scientists discovered that the thalamus—long assumed to be a mere relay station—plays a role in animal memory and ability to distinguish categories.[466] Specifically, by manipulating the activity of thalamus neurons in mice, scientists were able to control the animals' ability to remember how to find a reward. In the future, the thalamus could become a target for interventions to reduce cognitive deficits observed in mental illnesses, such as schizophrenia.

Molecular metabolism is important for understanding mechanisms for disease progression, as well as drug interventions. NIMH IRP scientists and NIMH-supported extramural collaborators uncovered the mechanisms behind the rapid antidepressant and anti-suicidal effects of ketamine, an anesthetic drug, in individuals with treatment-resistant depression. Results revealed that a byproduct of ketamine's chemical breakdown, and not ketamine itself, produces the antidepressant effects.[467] Identifying this mechanism is a crucial step in the drug development process and highlights the importance of basic science.

We have the amazing ability to sense and interpret the world surrounding us through vision, hearing, smell, taste, and touch. Our senses enrich our experience of the world around us. In order to experience these senses, we require a complex network of different types of tissues, receptors, cells, signaling pathways, and specific parts of the brain. If one of these network connections is off, it can affect a person's overall health and well-being.

[465] https://www.nimh.nih.gov/about/director/messages/2017/neural-circuits-research-how-and-why.shtml.
[466] https://www.nimh.nih.gov/news/science-news/2017/brain-relay-also-key-to-holding-thoughts-in-mind.shtml.
[467] https://www.nimh.nih.gov/news/science-news/2016/ketamine-lifts-depression-via-a-byproduct-of-its-metabolism.shtml.

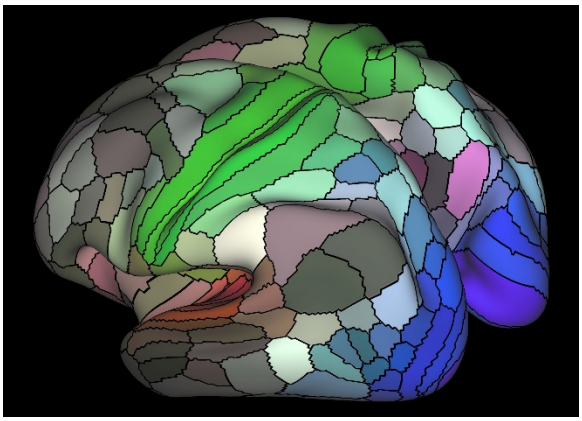

Figure 34. Map of brain cortex showing areas connected to the three main senses—hearing (red), touch (green) vision (blue), and opposing cognitive systems (light and dark). The map is based on data from resting state functional magnetic resolution imaging scans performed as part of the Human Connectome Project. Credit: Matthew Glasser, Ph.D., and David Van Essen, Ph.D., Washington University in St. Louis.

Most people rely on their eyes to see and make sense of the world around them. NEI-funded researchers were surprised to discover that intrinsically photosensitive retinal ganglion cells (ipRGCs) can influence our visual perception of the world. These cells detect light like other cells in the retina, but they were originally thought to use light only to regulate the body's internal clock, not provide any input into what we see. The researchers developed a new tool to selectively stimulate either the ipRGCs or the cone photoreceptors and found that in each case the stimuli produced activity in the primary visual cortex, the part of the brain that processes vision.[468] Moreover, study participants found the stimulus unpleasant, further providing evidence ipRGCs influence vision more than anyone previously realized. This new tool may be clinically valuable in cases involving excessive sensitivity to bright light.

The research community has long recognized the importance of the superior colliculus, a brain structure present in all vertebrates, in visual processing, but its exact role was unclear. NEI IRP researchers discovered that the superior colliculus is responsible for recognizing whether a new object enters the visual field. Using animal and mathematical models, researchers determined that the superior colliculus requires a specific threshold of neuronal activity before sending a signal to other parts of the brain that a new object in the visual field warrants a behavioral response.[469] The superior colliculus does not recognize what object is present but is a key intermediary between the eye and higher-order behavioral responses to the object.

[468] Spitschan M, et al. *Proc Natl Acad Sci* 2017;114(46):12291-6. PMID: 29087940.
[469] Herman JP, et al. Nat Neurosci 2018;21(12):1651-5. PMID: 30482945.

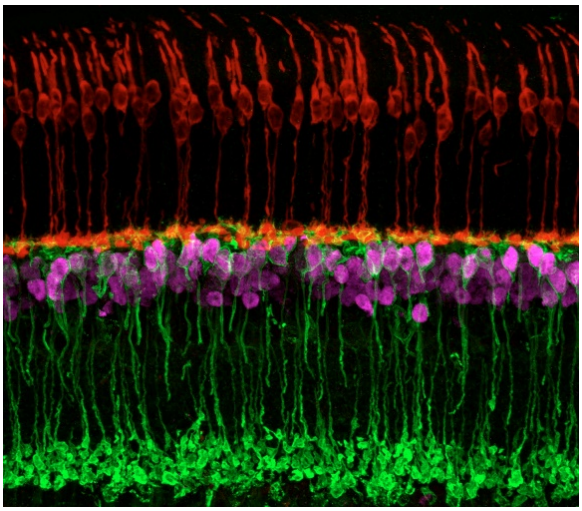

Figure 35. Neuronal circuits in the mouse retina. Cone photoreceptors (red) enable color vision; bipolar neurons (magenta) relay information further along the circuit; and a subtype of bipolar neuron (green) helps process signals sensed by other photoreceptors in dim light. Credit: Brian Liu and Melanie Samuel, Baylor College of Medicine, Houston.

Another aspect of visual processing involves eye movements. NEI-funded researchers showed that two well-established series of eye movements in freely moving rodents also take place in a similar way in humans. They showed that the grid-cell and border-cell operations can be used to find landmarks during brain scans.[470] Understanding humans' use of visual information in navigation is fundamental to developing rehabilitative strategies for visually impaired people.

The research community has long understood that the brain could rewire itself to compensate for lost vision, but how the brain does this remains a mystery, as does why some brain structures rework themselves to perform different functions. Recent work demonstrated that a part of the visual cortex, known as the visual word form area and known to have strong connectivity with language in sighted patients, was active during grammatical processing of spoken sentences in congenitally blind Braille readers but not in sighted readers of print.[471]

Hearing depends on a series of complex steps that change sound waves traveling through the air into the outer, middle, and inner ears into electrical signals. Our auditory nerve then carries these signals to the brain. NIDCD-supported scientists have discovered how to generate organoids from stem cells that functionally mimic human inner ear cells.[472] In addition, the organoids contained neurons, important to transmit signals from the ear to the brain, that formed connections with sensory cells. The scientists are currently using the human inner ear organoids to study how known genes that cause deafness interrupt normal development of the inner ear. They plan to start screening for drugs that could treat hearing and balance disorders using human inner ear organoids. As researchers try to find drugs to help treat hearing loss, other research teams have found a new way to explain the hearing loss caused by cisplatin, a

[470] Julian JB, et al. *Nat Neurosci* 2018;21(2):191-4. PMID: 29311745.
[471] Kim JS, et al. *J Neurosci* 2017;37(47):11495-504. PMID: 29061700.
[472] Koehler KR, et al. *Nat Biotechnol* 2017;35(6):583-9. PMID: 28459451.

powerful drug used to treat many forms of cancer.[473] Using a highly sensitive technique to measure and map cisplatin in mouse and human inner ear tissues, researchers found that forms of cisplatin build up in the inner ear.[474] They also found a region in the inner ear that could be targeted for efforts to prevent hearing loss from cisplatin.

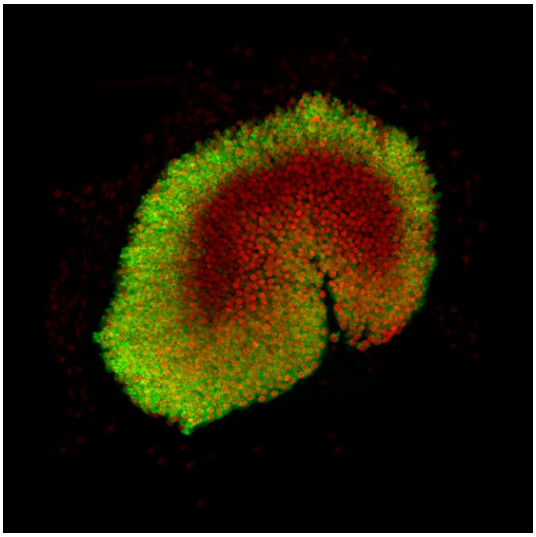

Figure 36. Hair cells (red) and associated supporting cells (green) in the sensory patch of a mouse utricle, part of the balancing apparatus of the inner ear. Credit: Joseph Burns, Ph.D., NIDCD.

Our sense of smell helps us enjoy life, but it is also a warning system, alerting us to such danger signals as a gas leak, spoiled food, or a fire. Any loss in our sense of smell can have a negative effect on our quality of life or be a sign of a health problem. Similarly, experiencing a smell for which there is no source, called a phantom odor, can also have a negative effect on quality of life. An NIH study found that 1 in 15 Americans (or 6.5 percent) over the age of 40 experience phantom odors.[475] The study is the first in the U.S. to use nationally representative data to examine the prevalence of and risk factors for phantom odor perception, and it could inform future research aiming to unlock the mysteries of phantom odors.

Problems with the sense of taste can have a big impact on life. Taste stimulates the desire to eat and therefore plays a key role in nutrition. The sense of taste also helps keep us healthy by helping us detect spoiled food or drinks. Stem cells in our tongues allow us to replace lost taste cells throughout life. NIDCD-supported scientists are learning how taste stem cells give rise to the various types of cells found within a taste bud, including taste receptors that detect sweet, sour, bitter, salty, or savory flavors. By isolating and growing taste stem cells into taste bud-like organoids, the team of scientists identified that genes relevant for cell division are expressed early, while taste-specific genes, as well as several genes not previously implicated in taste cell development and function, are expressed later.[476] These findings may

[473] https://www.nidcd.nih.gov/news/2017/nih-study-uncovers-clues-about-why-common-cancer-drug-causes-hearing-loss.
[474] Breglio AM, et al., *Nat Commun* 2017;8(1):1654.
[475] Bainbridge KE, et al. *JAMA Otolaryngol Head Neck Surg* 2018;144(9):807-14. PMID: 30128498.
[476] Ren W, et al. *Sci Rep* 2017;7(1):4004. PMID: 28638111.

help scientists learn how to restore taste cells lost after chemotherapy for head and neck cancers or to influence taste to help people choose to eat more nutritious foods.

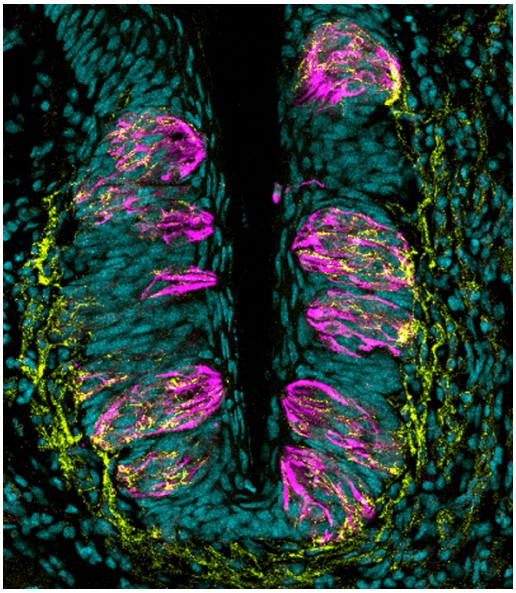

Figure 37. A structure on the tongue—a taste papilla—contains taste buds (pink) that send information through taste nerve fibers (yellow) to the brain. Each taste bud contains cells that respond to specific tastes—sweet, bitter, umami, salty, sour, or fat. Credit: Dany Gaillard, Ph.D., and Linda Barlow, Ph.D., University of Colorado Anschutz Medical Campus.

From infancy, we use our hands to explore and interact with our environment. Even before we begin using our hands to perform specific tasks, they play an important role in helping us to learn, communicate, and develop social bonds. Previously, work by NCCIH-funded researchers discovered that the protein Piezo2 is involved in detecting touch and sensations by sending signals through nerves in the skin to the brain. In this new study, a team of NCCIH- and NIDCR-funded researchers showed that the *Piezo2* gene, which encodes Piezo2 protein, guides the production of different forms of the protein, which may play roles in distinguishing such sensations as gentle touch, stretching, vibration, and pain.[477] These findings indicate that touch detection is regulated at the molecular level and produces distinct responses in different types of cells. Additional research on pain is described in the Chronic Pain subsection of the Chronic Diseases section of this chapter.

Multiple mechanisms exist for sensory specialization, or the process by which sensory nerve cells distinguish different types of sensations. Researchers have identified a class of sensory neurons—nerve cells that electrically send and receive messages between the body and brain—that can be activated by stimuli as precise as the pulling of a single hair.[478] Understanding basic mechanisms underlying these different types of responses will be an important step toward the rational design of new approaches to pain therapy.

[477] Szczot M, et al. *Cell Rep* 2017;21(10):2760-71. PMID: 29212024.
[478] Ghitani N, et al. *Neuron* 2017;95(4):944-54.e4. PMID: 28817806.

Quality sleep—and getting enough of it at the right times—is as essential to survival as food and water. Sleep is important to a number of brain functions, including how nerve cells (neurons) communicate with one another. In fact, the brain and body stay remarkably active during sleep. NIH-funded researchers reported connections between obstructive sleep apnea symptoms and thinning of the brain's cerebral cortex.[479] The researchers also discovered differences in these brain changes between men and women, which could help explain why women are more likely than men to have cognitive symptoms like depression, insomnia, and anxiety with obstructive sleep apnea.

The meninges are a collection of membranes that line the central nervous system and help protect brain and spinal cord tissue from various forms of injury. To understand how the meninges recover after a traumatic brain injury, NINDS IRP researchers used state-of-the-art imaging tools to watch in real time what happened in mouse meninges up to 1 week after traumatic brain injury.[480] The researchers discovered that a second injury within 1 day of the first traumatic brain injury terminated the meningeal repair process, but a second injury after a longer delay did not interfere with this process.[481] Additionally, this study provided important insights into the time course of and different cell types involved in cellular repair after traumatic brain injury.

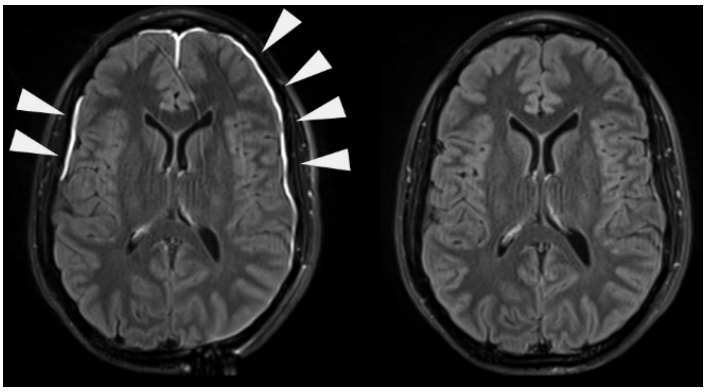

Figure 38. Damaged meninges: One day after head injury (left), bright dye along the edge of the brain suggests damage to the meninges, or the brain's protective lining. After 35 days (right), the dye no longer appears, indicating the meninges may have healed. Credit: Larry Latour, Ph.D., NINDS.

Scientists in the NIEHS Synaptic and Developmental Plasticity Group have discovered a novel mechanism by which certain memories may be formed in the brain. Their report provides the first evidence of a specific mechanism for encoding social and contextual information in a part of the brain known as the CA2 region of the hippocampus.[482] Additionally, IRP scientists won an innovation award for their work on the mechanisms underlying hippocampal CA2 resistance to injury, which focused on identifying the molecular mechanisms that allow certain regions of the brain to resist cell death after injury.[483]

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[479] Macey PM, et al. *PLoS One* 2018;13(3):e0193854. PMID: 29509806.
[480] https://www.nih.gov/news-events/news-releases/nih-scientists-watch-brains-lining-heal-after-head-injury.
[481] Russo MV, et al. *Nat Immunol* 2018;19(5):442-52. PMID: 29662169.
[482] Alexander GM, et al. *Nat Commun* 2016;7:10300. PMID: 26806606.
[483] https://factor.niehs.nih.gov/2017/3/feature/feature-1-innovation/index.htm.

The hippocampus is responsible for aiding in memory, and it is closely connected to the amygdala, which mediates fear and other emotions. A 2016 paper by NIDA researchers suggests that the amygdala central nucleus plays a role in predicting reward value and allocating work accordingly.[484,485] Rats expecting a reward show activation in the amygdala central nucleus and work hard to get the reward. Once the rats learned that the reward was absent or less than they expected, activation in the amygdala central nucleus declined and reward-driven actions dropped. These findings suggest that the amygdala central nucleus helps manage expectations and provide insights into the underlying mechanisms of addiction treatments that aim to stop drug-taking, as well as other treatments that reduce, but do not eliminate, rewards (for example, overeating).

When the brain is healthy, it functions quickly and automatically, but when problems occur, the results can be devastating. Some 50 million people in this country—one in five—suffer from damage to the nervous system. NIDCD supports research to help understand the neurological basis of why some individuals with post-stroke chronic aphasia, a disorder that results from damage to portions of the brain that are responsible for language, improve with speech treatment while others show little response. Significant advances in imaging technology have improved the understanding of the complex actions that take place in the part of the brain controlling human speech and have allowed mapping of the functional connections of the brain that are responsible for speech control. In one NIDCD-sponsored study, researchers are using advanced imaging and a new analytical approach to understand what areas of the brain are important for treatment-induced speech recovery.[486] They found that recovery is based on how well the language networks of the brain can restructure after stroke. These findings may help guide treatment decision-making for individuals with chronic aphasia caused by a stroke. The same imaging, analysis, and treatment strategies can also be applied to other conditions, such as post-stroke motor rehabilitation, neurodegeneration, or traumatic brain injury.

Identifying Risk Factors

A health risk is the chance or likelihood that something will harm or otherwise affect a person's health. Several characteristics, called risk factors, affect whether a person's health risks are high or low. Personal health risk factors include age, sex, family health history, lifestyle, and more. Some risk factors, such as genes or ethnicity, cannot be changed. Others—such as diet, physical activity, and seatbelt use—are within a person's control. Whether or not we are at risk for a disease depends on changes in our genes and on the effects of our environment. Understanding risk factors can lead to prevention and early detection of disease.

Increasing age is the most important known risk factor for Alzheimer's disease. The number of people with Alzheimer's disease doubles every 5 years beyond age 65. About one-third of all people age 85 and older may have Alzheimer's disease. The causes of late-onset Alzheimer's disease, the most common

[484] https://www.drugabuse.gov/news-events/news-releases/2016/08/brain-region-may-manage-reward-expectations-responding.
[485] Iordanova MD, et al. *Nat Commun* 2016;7:12330. PMID: 27531638.
[486] McKinnon ET, et al. *Ann Neurol* 2017;82(1):147-51. PMID: 28628946.

form, probably include a combination of genetic, lifestyle, and environmental factors. The importance of any one of these factors in increasing or decreasing the risk of developing Alzheimer's disease may differ from person to person.

Genetics

NIA supports several initiatives to identify genes involved in the development of AD/ADRD:

- The Alzheimer's Disease Sequencing Project (ADSP), which aims to pursue rare variants in a range of different populations, including those that have been underrepresented in sequencing studies.[487] Leveraging the existing infrastructure of the ADSP, the Follow-Up Study aims to generate whole genome sequence data in African American, Asian American, Hispanic, and Native American populations.
- The Genome Center for Alzheimer's Disease (GCAD), funded by NIA in spring 2016, serves as a national resource for integrating and analyzing Alzheimer's disease genetic data, with the goal of identifying genetic and genomic factors for potential therapeutic approaches and prevention.[488] GCAD supports a multidisciplinary attack on AD/ADRD.
- The NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) plays an important role in understanding the genetic and cellular underpinnings of Alzheimer's disease by archiving, processing, and distributing data related to the disease's genetics and genomics.[489] Recently, NIAGADS augmented its ability to share genetic data with the research community by moving all ADSP data to a secure cloud-based environment with a capacity for investigator analysis, as well as undertaking a major effort to harmonize phenotypic data across multiple types of studies, including imaging and biomarker studies. In addition, NIAGADS released Genomics Database version 3.1, which allows investigators to compare their own data with that of the ADSP and analyze it based on gene function and cellular pathways.

The *APOE4* variant of the *APOE* gene is the strongest known genetic risk factor for late-onset Alzheimer's disease. In a study in mice, NINDS-supported researchers discovered a link between ApoE4, the protein encoded by the *APOE* gene, and the toxic accumulation of another protein, tau.[490] This finding suggests that reducing ApoE protein in the brain could have potential as a novel treatment strategy for Alzheimer's disease. Other risk factors can act in synergy with the *APOE4* variant. New findings from the Multi-ethnic Study of Atherosclerosis suggest that sleep-disordered breathing may be a modifiable risk factor for cognitive decline.[491] Study participants (mean age 68) who had sleep apnea performed worse on cognitive

[487] https://www.niagads.org/adsp/content/about.
[488] http://www.adgenomics.org/.
[489] https://www.niagads.org/adsp/content/home.
[490] Shi Y, et al. *Nature* 2017; 549(7673):523-27. PMID: 28959956.
[491] https://www.medpagetoday.org/geriatrics/sleepdisorders/66802?xid=nl_mpt_DHE_2017-07-22&eun=g453673d0r&pos=1.

tests than those without sleep-disordered breathing, and performance was worse still for those who both had sleep-disordered breathing and carried the *APOE4* variant of *APOE*.[492]

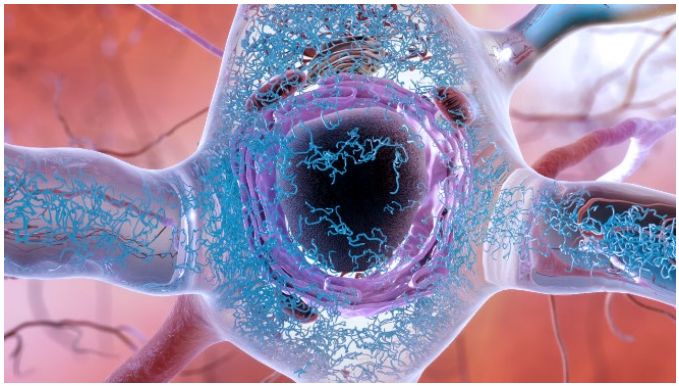

Figure 39. Abnormal accumulations of a protein called tau can collect inside neurons, forming tangled threads and eventually harming the synaptic connection between neurons. Credit: NIA.

Like Alzheimer's disease, a clear risk factor for Parkinson's disease is age. Although most people with Parkinson's disease first develop symptoms at about age 60, about 5 to 10 percent of people with Parkinson's disease have early-onset disease, which begins before the age of 50. Early-onset forms of Parkinson's disease are often, but not always, inherited, and some forms have been linked to specific gene mutations. Although some cases of Parkinson's disease appear to be hereditary, and a few can be traced to specific genetic mutations, in most cases the disease occurs randomly and does not seem to run in families. Many researchers now believe that Parkinson's disease results from a combination of genetic factors and environmental factors, such as exposure to toxins.

As part of a worldwide collaboration among many Parkinson's disease research groups, NIA IRP investigators performed the largest genetic study of Parkinson's disease to date, involving analysis of 11.4 million SNPs in 37,700 cases, 18,600 UK Biobank proxy cases (for subjects having a parent with Parkinson's disease), and 1.4 million controls.[493,494] The study identified 92 Parkinson's disease–associated genetic loci, including 39 novel ones. Subsequent analyses showed that only a subset of these genetic variants also have a significant effect on the age of onset of Parkinson's disease. This provides a compelling picture for defining differences between genetic risk factors for age at onset or frank risk for disease. To that point, NIH-funded researchers analyzed Medicare claims data of more than 200,000 people to develop an algorithm to predict whether a patient will one day be diagnosed with Parkinson's disease.[495] The algorithm relies on information in patients' medical records, such as tests and diagnoses of various medical conditions.

Family studies that include identical twins, fraternal twins, adoptees, and siblings suggest that as much as half of a person's risk of becoming addicted to nicotine, alcohol, or other drugs depends on their genetic

[492] Johnson DA, et al. *Ann Am Thorac Soc* 2017;14(11):1697-1705. PMID: 28731362.
[493] https://www.biorxiv.org/content/10.1101/388165v3.
[494] Blauwendraat C, et al. *Mov Disord* 2019;34(6):866-75. PMID: 30957308.
[495] https://medicine.wustl.edu/news/medical-history-can-point-earlier-parkinsons-disease-diagnosis/.

makeup. Finding the biological basis for this risk is an important avenue of research for scientists trying to solve the problem of drug addiction. A genetic variant found only in people of African descent significantly increases a smoker's preference for cigarettes containing menthol, a flavor additive.[496] The variant of the *MRGPRX4* gene is five to eight times more frequent among smokers who use menthol cigarettes than other smokers, according to an international group of researchers supported by FDA and NIH.[497] This multiethnic study is the first to look across all genes to identify genetic vulnerability to menthol cigarettes.

In many cases, it is believed that genetic factors play a role in the risk and causes of some seizure-related disorders and a number of the epilepsies. In 2017, NINDS released a FOA inviting applications to the Epilepsy CWOW program.[498] The goal of this program is to advance understanding of genetic factors in the epilepsies and accelerate development of diagnostics and individualized treatments. Recently funded projects are studying genetic factors in sudden death in epilepsy, channelopathy-associated epilepsy syndromes, and epilepsy syndromes that arise after traumatic brain injury, also known as post-traumatic epilepsy.

Environment

The epilepsy syndromes have a wide range of severities, precipitating causes, comorbidities, and treatment outcomes. Nodding syndrome is a form of epilepsy with an unknown cause that occurs in children in East Africa.[499] Researchers in the NIH IRP examined the serum and cerebrospinal fluid of children with Nodding syndrome and found neurotoxic antibodies specific for molecules produced by *Onchocerca volvulus*, a parasitic worm known to cause river blindness. Their findings support the hypothesis that Nodding syndrome is an autoimmune disorder caused by exposure to *O. volvulus*.

As emerging evidence links toxicant exposure with central nervous system and behavioral changes consistent with disorders ranging from schizophrenia to depression, it is important to incorporate environmental factors in the study of these diseases to allow for better preventive and therapeutic strategies. NIEHS held a workshop to explore the biological mechanisms behind environmental risks for psychiatric disorders.[500] The workshop brought together experts in the fields of psychiatry, fundamental neuroscience, human genetics, immunology, and environmental health sciences to identify common pathways and mechanisms implicated in psychiatric disorders that are potential targets of environmental exposures. The organizers are generating a report to be published on the state of the science and to help determine the most appropriate and productive directions for research in the area of environmental factors in risk for mental disorders.

Additional efforts are led by NIEHS to investigate the role of per- and polyfluoroalkyl substances (PFAS) in disease; approximately 40 active NIEHS research grants are examining PFAS. Some NIEHS-funded grantees are exploring a potential link between PFAS and behavioral disorders, such as attention deficit

[496] https://www.nidcd.nih.gov/news/2019/researchers-find-genetic-vulnerability-menthol-cigarette-use.
[497] Kozlitina J, et al. *PLoS Genet* 2019;15(2):e1007916. PMID: 30768591.
[498] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-18-001.html.
[499] Johnson TP, et al. *Sci Transl Med* 2017;9(377). PMID: 28202777.
[500] https://www.niehs.nih.gov/news/events/pastmtg/2017/biological-mechanisms/index.cfm.

hyperactivity disorder, while others are evaluating the potential adverse health risks of PFAS and other chemicals on neurobehavioral development and immune function.[501] An Office of Science and Technology Policy–sponsored federal information exchange was held on the NIH campus in February 2018. This meeting resulted in the formation of ongoing interagency collaborations on exposure, toxicology, and risk communication.

Behavioral

Behaviors, including diet and physical activity, are largely within a person's control and can confer or reduce risk. For example, a diet rich in salt is linked to an increased risk of cerebrovascular diseases and dementia, and previous studies supported by NINDS have also described mechanisms by which dietary salt may lead to the development of multiple sclerosis (MS) and other autoimmune diseases. In 2018, NINDS-supported scientists identified a novel gut–brain signaling pathway linking dietary salt to brain function via TH17 cells, a type of immune cell found in the small intestine.[502] The study revealed that TH17 cells respond to excessive dietary salt by releasing a substance, IL-17, that reaches brain cells and impairs cognitive function, suggesting that targeting the IL-17 pathway may be an effective treatment strategy for reversing the harmful effects of a high-salt diet on the brain.[503]

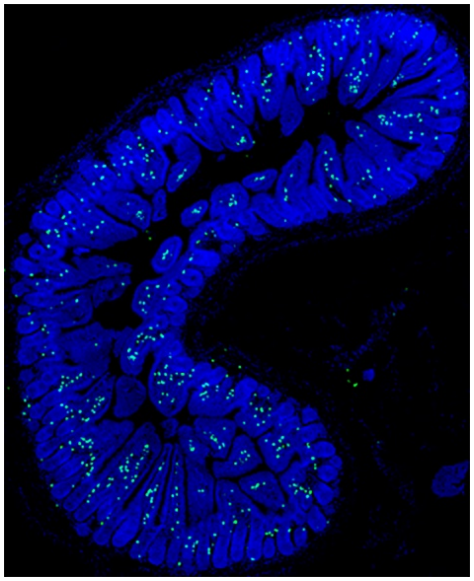

Figure 40. Immune Cells Secreting IL-17 Molecule. Credit: Iadecola Lab, Weill Cornell Medicine, NYC.

Chronic traumatic encephalopathy (CTE) is a progressive neurodegeneration associated with repetitive head trauma. In a case series of 202 deceased National Football League (NFL) football players, researchers examined past clinical evaluations and evaluated post-mortem brain tissue.[504] The researchers found that nearly all the former NFL players had CTE pathology, and the pathology was frequently severe, suggesting

[501] https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2018/june/presentations/10devito_508.pdf.
[502] https://www.nih.gov/news-events/news-releases/hold-salt-gut-reaction-may-impair-brains-mice.
[503] Faraco G, et al. *Nat Neurosci* 2018; 21(2):240-9. PMID: 29335605.
[504] Mez J, et al. *JAMA* 2017; 318(4):360-70. PMID: 28742910.

that CTE may be related to prior participation in football and that a high level of play may be related to substantial disease burden.

Focusing on Prevention

Human brain development starts soon after conception and continues into early adulthood. During development, the brain is susceptible to biological and environmental factors that can lead to neurodevelopmental problems. The NIH ICs with neuroscience portfolios focus on prevention of brain disorders and injuries throughout the lifetime of an individual to reduce burden and improve quality of life. Brain disorders and injuries, due to the nature of the brain, are complex, and the best strategies to prevent or delay them may turn out to be a combination of measures.

Nearly 10 percent of all babies worldwide are born preterm, meaning before the end of the 37th week of pregnancy. Preterm infants are more likely to have cognitive difficulties and trouble in school, possibly because of disruptions in the way that the brain is wired before or shortly after birth.

Two trials funded by NINDS are assessing erythropoietin to prevent death and neurodevelopmental disability in infants born premature. Erythropoietin is an inflammatory signaling molecule with neuroprotective effects demonstrated in animal models of neonatal brain injury, and it is commercially available, relatively inexpensive, and safe in neonates. The Preterm Erythropoietin Neuroprotection Trial (PENUT Trial) is testing whether early high-dose erythropoietin treatment in extremely low gestational age newborns will decrease death or severe neurodevelopmental disability, including cerebral palsy, measured at 2 years corrected age.[505] The High-dose Erythropoietin for Asphyxia and Encephalopathy Trial will determine whether erythropoietin therapy combined with therapeutic hypothermia will reduce death and neurodevelopmental impairment in infants 36 weeks of gestational age and older who have moderate or severe hypoxic-ischemic encephalopathy, or brain damage due to low blood and oxygen supply to the brain.[506]

Recent NINDS-funded research showed that electroencephalogram biomarkers can predict seizure activity prior to onset in infants with tuberous sclerosis complex, a genetic disease that causes benign tumors to grow in the brain and other vital organs. The NINDS Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) trial will use electroencephalogram biomarkers to test whether presymptomatic treatment with the antiseizure medication vigabatrin prevents the development of epilepsy in infants with tuberous sclerosis complex, as well as whether treatment improves cognitive and behavioral outcomes or reduces the risk of developing ASD.[507]

Although the foundation of a functioning brain is assembled prenatally, brain function itself continues to develop after birth, driven largely by sensory input. Prior to the establishment of a federal universal newborn infant hearing screening program in 1999, less than 10 percent of newborns in the U.S. were

[505] https://projectreporter.nih.gov/project_info_description.cfm?aid=9268807&icde=34717210.
[506] https://projectreporter.nih.gov/project_info_description.cfm?aid=9504464&icde=0.
[507] https://projectreporter.nih.gov/project_info_description.cfm?aid=9103780&icde=42391735.

screened for hearing loss. As a result, 47 percent of children born with hearing loss were not diagnosed until their third birthday or later, missing a crucial period for language acquisition.

On October 18, 2017, the President signed into law the *Early Hearing Detection and Intervention Act* (P.L. 115-71) to strengthen early hearing screening programs for infants and children. The law amends the *PHS Act* to reauthorize until 2022 a federal program administered by HHS.[508] Three HHS agencies—CDC, NIH, and the Health Resources and Services Administration (HRSA)—will continue a long-standing partnership to coordinate and advance a national program for the early identification and diagnosis of hearing loss and intervention services for deaf and hard-of-hearing newborns and infants.[509,510] In addition, the law authorizes specific changes to the federal program, such as expanding the program to include young children, under the age of 3, who are at risk of losing their hearing during childhood from infection, harmful noise exposure, or genetic causes. These types of collaborations are critical to improving outcomes for affected children.

The developing brain relies on environmental and endogenous stimuli to help it determine which connections should be pruned and which should not. Toxic exposures can interfere with the brain's ability to distinguish important connections from unimportant ones, altering development. For example, lead can cause neurons to fire spontaneously in the absence of a proper signal. University of Michigan Children's Environmental Health Center Community Outreach and Translation Core (COTC) developed and disseminated educational materials on lead-mitigation tactics for parents to use at home and educators to train other families in the community.[511] In collaboration with the University of Michigan's COTC, the Public Health Practice Office and community partners in Flint, Michigan, developed training materials on lead-shielding nutrients and tips for incorporating them into the diet of children ages 2 to 6 years old.

According to U.S. Census projections, by 2030, all baby boomers—defined as those born between 1946 and 1964—in the U.S. will be older than age 65, meaning that one in every five Americans will be at retirement age. A large sector of this population is currently (as of 2018) between the ages of 54 and 64, and described by the CDC, AARP, and American Medical Association (AMA) as mid-life stage adults. As this large sector of the population ages, it faces an increasing need for clinical and other preventive services to support maintenance of good health into older age. To this point, *Mind Your Risks* is a public health campaign that educates people with high blood pressure about the importance of controlling blood pressure during the mid-life stage to help reduce the risk of having a stroke and possibly developing dementia later in life.[512]

Stroke prevention is a multipronged approach—some efforts focus on reducing risk for stroke initially, whereas others focus on reducing risk for recurrent strokes. In a clinical trial funded by NINDS, researchers discovered that combination antiplatelet therapy with clopidogrel and aspirin may reduce the rate of

[508] https://www.nidcd.nih.gov/news/2017/new-law-early-hearing-screening-infants-and-children.
[509] https://www.cdc.gov/ncbddd/hearingloss/index.html.
[510] https://mchb.hrsa.gov/maternal-child-health-initiatives/early-hearing-detection-and-intervention.html.
[511] https://sph.umich.edu/cehc/outreach/index.html.
[512] https://www.mindyourrisks.nih.gov/.

recurrent stroke during the first 3 months after a minor ischemic stroke or transient ischemic attack.[513] Those who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days than those who received aspirin alone.

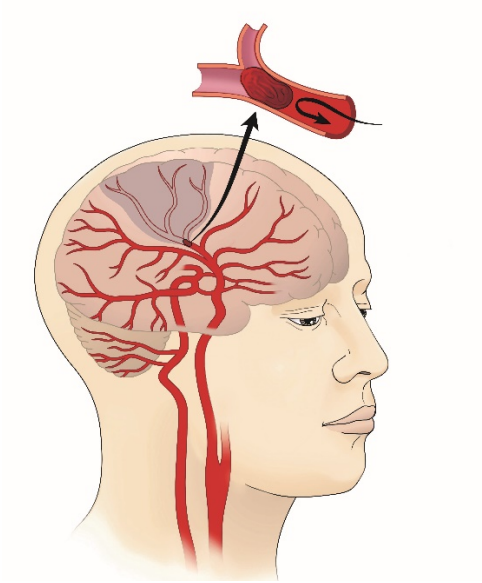

Figure 41. Illustration of an ischemic stroke, which occurs when a brain blood vessel gets blocked. The gray area represents brain tissue that is not receiving nutrients as a result of the stroke. Credit: NINDS.

Another risk factor for stroke and myocardial infarction is insulin resistance, which raised the possibility that pioglitazone, a drug that improves insulin sensitivity, might benefit patients with cerebrovascular disease. In a NINDS-supported trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or transient ischemic attack, the risk of stroke or myocardial infarction was found to be lower among patients who received pioglitazone than among those who received placebo.[514] Although pioglitazone was also associated with a lower risk of diabetes, it came with higher risks of weight gain, edema, and fracture.

As life expectancy increases, and as many people engage in longer working lives, the need to promote healthy aging is imperative and requires innovative collaborative networks. The overall goal of NINDS' Stroke Preclinical Assessment Network (SPAN) program is to create a virtual network to support late-stage preclinical studies of potential neuroprotective strategies.[515] SPAN researchers will test potential strategies to either improve long-term functional outcome or extend the therapeutic window of intervention in animal models of transient cerebral ischemia. Applicants for SPAN program sites must propose a promising neuroprotective intervention to be tested within SPAN; awarded sites will test up to six interventions in parallel, including their own. If successful, this network will accelerate the

[513] Johnston SC, et al. *N Engl J Med* 2018. PMID: 29766750.
[514] Mez J, et al. *JAMA* 2017;318(4):360-70. PMID: 28742910.
[515] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-18-033.html.

identification of the most promising neuroprotective therapies for future pivotal clinical trials and span the gap between preclinical and clinical testing, in a cost- and time-effective fashion.

In 2018, NIA started a new program, Towards Implementing Novel Training Methods to Enhance Cognition in Aging.[516] The program supports three planning awards to develop and finalize innovative protocols, such as video games for cognitive enhancement, for well-powered cognitive training intervention trials to remediate or prevent age-related cognitive decline, as well as to prevent or delay the onset of mild cognitive impairment and dementia. These cooperative agreements provide up to 2 years of funding to develop plans to better understand the necessary components and mechanisms of cognitive training.

Improving Detection and Diagnosis

Diagnostic tests and procedures are vital tools that help physicians confirm or rule out a neurological disorder or other medical condition. A century ago, the only way to make a definite diagnosis for many neurological disorders was to perform an autopsy. Today, new instruments and techniques allow scientists to assess the living brain and monitor nervous system activity as it occurs. Doctors now have powerful and accurate tools to better diagnose disease and to test how well a particular therapy may be working.

Diagnostic Imaging

Perhaps the most significant changes during the past 10 years have occurred in genetic testing and diagnostic imaging. Improved imaging techniques provide high-resolution images that allow physicians to view the structure of the brain. Specialized imaging methods can visualize changes in brain activity or the amounts of particular brain chemicals. Scientists continue to improve these methods to provide more detailed diagnostic information.

A diagnosis of ASD requires a doctor to observe a child's behavior and development. ACE and NICHD-supported researchers reported that brain imaging may help predict ASD among high-risk infants as young as 6 months of age.[517] The team found that brain-related changes occurred before behavioral symptoms emerged.[518] These changes may be detected through functional connectivity MRI. Although the findings are early stage, the study suggests that in the future, neuroimaging may be a useful tool to diagnose ASD or help health care providers better evaluate a child's risk of developing the disorder.

Doctors use several methods and tools to help diagnose Alzheimer's disease, including testing memory, problem solving, attention, counting, and language, as well as performing standard medical tests and brain scans. NIA IRP investigators have showed for the first time that glucose concentration was higher in the brains of Alzheimer's disease patients than in people of the same age without Alzheimer's disease.[519]

[516] https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-18-031.html.
[517] https://www.nichd.nih.gov/newsroom/releases/060717-autism-MRI.
[518] Emerson RW, et al. *Sci Transl Med* 2017;9(393). PMID: 28592562.
[519] Mullins R, et al. *Ann Clin Transl Neurol* 2018;5(3):262-72. PMID: 29560372.

The measures were obtained through standard magnetic resonance spectroscopy (MRS) scanners, which are noninvasive (as opposed to lumbar punctures), do not involve radiation (as opposed to PET scans), and distinguish Alzheimer's disease patients from cognitively healthy people better than MRI scans. MRS measurements of brain glucose concentration could potentially be used in the future as a noninvasive method to help diagnose Alzheimer's disease and to provide an outcome measure in clinical trials to help researchers better assess Alzheimer's disease interventions.

Primary progressive aphasia is a neurodegenerative disease associated with language decline. The gold standard for diagnosing primary progressive aphasia is by assessing atrophy, or shrinkage, within the brain using traditional structural MRI. Early-stage disease does not display this atrophy, so making a diagnosis and starting early treatment is difficult. NIDCD-funded scientists provided proof of concept for a way to diagnose primary progressive aphasia earlier by using two brain imaging techniques: functional MRI and traditional structural MRI.[520] The researchers were able to observe and measure reduced functional connectivity in the language networks of the brain in individuals who had pronounced language difficulties but no significant signs of brain atrophy. This advance may help physicians diagnose and treat individuals with primary progressive aphasia earlier, potentially allowing better communication outcomes.

The scientific method is built on the premise that every answer yields another question. A team of NINDS IRP researchers found that the chemical gadolinium, routinely given to stroke patients undergoing brain scans, can leak into their eyes and highlight areas of brain damage.[521] In healthy individuals, gadolinium remains in the blood stream and is filtered out by the kidneys. However, when someone has experienced damage to the blood–brain barrier, which controls whether substances in the blood can enter the brain, gadolinium leaks into the brain, creating bright spots that mark the location of brain damage.[522] The findings raise the question of whether there is something that can be observed in the eye that would help clinicians evaluate the severity of a stroke and guide them on how best to help patients.

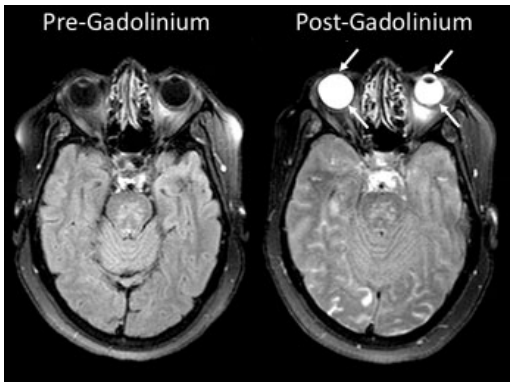

Figure 42. Research into curious bright spots in the eyes on stroke patients' brain images could one day alter the way these individuals are assessed and treated. A team of scientists at NIH found that a chemical routinely given to stroke patients undergoing brain scans can leak into their eyes, highlighting those areas and potentially providing insight into their strokes. Credit: Stroke Lab, NINDS.

[520] Bonakdarpour B, et al. *Alzheimer Dis Assoc Disord* 2017; 31(2):101-6. PMID: 28288010.
[521] https://www.nih.gov/news-events/news-releases/eye-could-provide-window-brain-after-stroke.
[522] Hitomi E, et al. *Neurology* 2018;90(11):e915-23. PMID: 29438039.

Biomarkers

Like advances in brain imaging, advances in biomarkers—defined characteristics used as indicators of normal biological processes, pathogenic processes, or responses to a therapeutic intervention—during the past decade have led to exciting new findings. Biomarkers are recognized as essential tools for the development of therapeutics, allowing improved and better informed clinical trial design through indicators of target engagement and those that enable patient stratification. In addition, biomarkers can facilitate the evaluation of therapeutic intervention on disease progression or recurrence.

Annually, millions of individuals experience a mild traumatic brain injury through falls, sports injuries, motor vehicle accidents, and many other causes. Brain scans, such as CT and MRI, can be used to detect traumatic brain injury and assess some of the small changes that can occur in the brain, such as neuron axonal injury. However, a blood-based test that can detect milder forms of brain injury with an equally accurate, less expensive, and faster turnaround is an attractive alternative. Researchers have shown that measuring blood levels of glial fibrillary acidic protein[523] or tau may be useful in distinguishing certain subgroups of traumatic brain injury. Concussions are a mild subgroup of traumatic brain injury, and millions of sports-related concussions occur each year in the U.S. NICHD-supported researchers reported that a blood test for the protein tau, taken within 6 hours of a concussion, can identify athletes who need more recovery time.[524] In the future, such a test could provide objective information to better inform athletes, trainers, and physicians about potential recovery times and when it is safe to return to play.

In addition to blood tests, gene-based tests are also being developed for traumatic brain injury. Scientists conducted a series of studies to determine the role of gene activity in injury, recovery, and symptoms following blast-induced traumatic brain injury in active-duty military personnel. Comparing those individuals with a record of blast-induced traumatic brain injury (or moderate blast exposure) to control participants without traumatic brain injury, the researchers identified genes that were regulated or expressed differently in personnel with traumatic brain injury.[525] Their findings provide a roadmap for characterizing and measuring the symptoms and effects of blast-induced traumatic brain injury acutely and in the months and years following a blast injury. These findings also establish a critical pathway toward the accurate diagnosis of blast-induced traumatic brain injury and for predicting the trajectory of recovery in military personnel.

Those who experience traumatic brain injury, such as from a sports-related concussion or blast injury, and who experience a subsequent injury before fully recovering from the first injury are at high risk of developing long-term cognitive and health problems. Cognitive impairment is caused most commonly by Alzheimer's disease, but can also be caused by diseases of the brain's blood vessels, particularly the network of small blood vessels that supply all parts of the brain. In 2017, NINDS collaborated with NIA to launch the MarkVCID program, a consortium of U.S. academic medical centers focused on identifying and validating biomarkers for the small-vessel diseases of the brain that produce vascular contributions to

[523] Gill J, et al. *Neurology* 2018;91(15):e1385-9. PMID: 30209234.
[524] Gill J, et al. *Neurology* 2017;88(6):595-602. PMID: 28062722.
[525] Gill J, et al. *Neurol Genet* 2017;3(5):e186. PMID: 28975156.

cognitive impairment and dementia (VCID).[526] MarkVCID comprises seven project sites and one coordinating center, each funded by 5-year grants from NINDS. The goal of the program is to deliver small-vessel VCID biomarkers that are ready for Phase II and Phase III clinical trials.

By the time clinical symptoms of Alzheimer's disease appear, extensive neuronal loss has already occurred. Current methods for detecting Alzheimer's disease characteristic pathology in the brain include imaging and cerebrospinal fluid analysis, but these tests are expensive and cumbersome. A team of NIH scientists, led by NIAID, developed an assay to improve the early diagnosis of Parkinson's disease and dementia with Lewy bodies, which correctly excluded all controls with Alzheimer's disease.[527,528] This suggests that more practical blood-based tests are feasible for diagnosis of neurodegenerative diseases. NIA-supported researchers found that measuring the ratio of two subtypes of amyloid-beta in blood plasma may be one such inexpensive, minimally invasive test.[529] In addition, NIA investigators developed a novel framework to identify brain and blood metabolites associated with disease pathology and progression in prodromal and preclinical Alzheimer's disease.[530,531]

In 2018, NIH launched the Accelerating Medicines Partnership for Parkinson's Disease (AMP-PD), which is a public–private partnership that will leverage existing cohorts and biomarkers resources, including the NINDS Parkinson's Disease Biomarker Program, Michael J. Fox Foundation (MJFF) Parkinson's Progression Marker Initiative, BioFIND (jointly funded by NINDS and MJFF), and Harvard Biomarker Study, to perform large-scale analyses of genes, gene transcription, and proteins to identify and validate biomarkers and new therapeutic targets for Parkinson's disease.[532] A critical component of this partnership among NINDS, Celgene, GlaxoSmithKline, MJFF, Pfizer, Sanofi, Verily, FDA, and the FNIH is that data and analyses will be publicly accessible to the broad biomedical community, hopefully facilitating biomarker discoveries for years to come.

Neurodegeneration can appear differently for each disease. Neurodegeneration in Fragile X–associated tremor/ataxia syndrome (FXTAS) is indicated by white-matter lesions in the brain; however, the degree of neurodegeneration seen in brain MRI images often does not match the severity of a person's symptoms. NICHD-supported researchers developed a blood test to measure mitochondrial activity in white blood cells, which correlated with neurodegeneration as indicated by the degree of total white-matter lesions in specific parts of the brain.[533] These findings provide insights into how neurodegeneration may be tracked in individuals with the *FMR1* premutation as they progress toward developing FXTAS.

Using the NIH Toolbox Cognitive Battery, NICHD- and NCATS-supported researchers measured working memory, processing speed, and vocabulary in patients with intellectual disabilities to assess cognitive

[526] https://markvcid.partners.org/.
[527] https://www.niaid.nih.gov/news-events/nih-scientists-adapt-new-brain-disease-test-parkinsons-dementia-lewy-bodies.
[528] Groveman BR, et al. *Acta Neuropathol Commun* 2018;6(1):7. PMID: 29422107.
[529] Ovod V, et al. *Alzheimers Dement* 2017;13(8):841-9. PMID: 28734653.
[530] Varma VR, et al. *PLoS Med* 2018;15(1):e1002482. PMID: 29370177.
[531] Shi L, et al. *J Alzheimers Dis* 2018;62(3):1181-98. PMID: 29562526.
[532] https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/parkinsons-disease.
[533] Loesch DZ, et al. *Neurodegener Dis* 2017;17(1):22-30. PMID: 27602566.

function and compare each patient's performance to peers from the general population.[534] Considering the findings of three preliminary studies together, the researchers showed that the NIH Toolbox Cognitive Battery has potential for assessing important parts of cognitive function in patients with intellectual disabilities, and several tests may be useful for tracking responses to interventions.

Many people worry about becoming forgetful, concerned that forgetfulness is the first sign of Alzheimer's disease, but not all people with memory problems have Alzheimer's disease. Other causes for memory problems can include aging, medical conditions, emotional problems, mild cognitive impairment, or another type of dementia. The goal of the Detecting Cognitive Impairment, Including Dementia (DetectCID) consortium is to establish, test, and validate methods for detecting cognitive impairment in the general public, including health disparities populations.[535] Initially, the consortium-funded projects will focus on developing and standardizing approaches that can be applied broadly across patient populations in the U.S. The second phase, which is expected to begin in 2020, will focus on testing and optimizing validated methods across multiple consortium sites.

Advancing Treatment

Simply described, the goal of NIH research is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability. However, neurological and neuropsychiatric disorders are still left with very few effective treatments.

Molecular Interventions

Genetic methodologies are having a rapidly increasingly impact on studies of the normal and diseased nervous system. To date, more than 200 genes that cause or contribute to neurological disorders have been identified. It is essential that neuroscientists exploit the power of modern molecular genetics and use the information becoming available from sequencing of the human genome. The NINDS Cooperative Research to Enable and Advance Translational Enterprises for Biotechnology Products and Biologics (CREATE Bio) program is dedicated to biotechnology product- and biologics-based therapies, which broadly include such modalities as peptides, proteins, oligonucleotides, gene therapies, and cell therapies, as well as novel emerging modalities.[536] The program includes two tracks: The first is the Optimization Track, which supports optimization to obtain a candidate appropriate for entering the second track, the Development Track, which supports investigational new drug–enabling studies for the candidate, as well as early-phase clinical trials.

Genome editing (also called gene editing) is a group of technologies that give scientists the ability to change an organism's DNA. These technologies allow genetic material to be added, removed, or altered

[534] Hessl D, et al. *J Neurodev Disord* 2016;8(1):35. PMID: 27602170.
[535] https://www.detectcid.org/.
[536] https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/CREATE-BIO.

at particular locations in the genome. Genome-editing technologies present an exciting prospect for treatments and possibly even cures for these diseases.

Antisense oligonucleotide therapies are an example of gene editing and use sequences of the letters in the genetic code designed to bind specific regions of RNA in order to modify gene expression. NINDS has supported research to develop antisense oligonucleotide therapies for neurological disorders, including spinal muscular atrophy, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, and other neurodegenerative disorders. In late 2016, FDA approved nusinersen, an antisense oligonucleotide therapy, for spinal muscular atrophy. NINDS and other ICs contributed to nusinersen's development by supporting research that focused on the disease's genetic cause and mechanisms, identified a treatment strategy and target, and facilitated later-stage translational and clinical research.[537] Researchers are also investigating antisense oligonucleotide therapy to target ataxin-2 in spinocerebellar ataxia type 2, where it delayed onset of symptoms in mouse models,[538] and amyotrophic lateral sclerosis, where it significantly improved survival in a mouse model.[539]

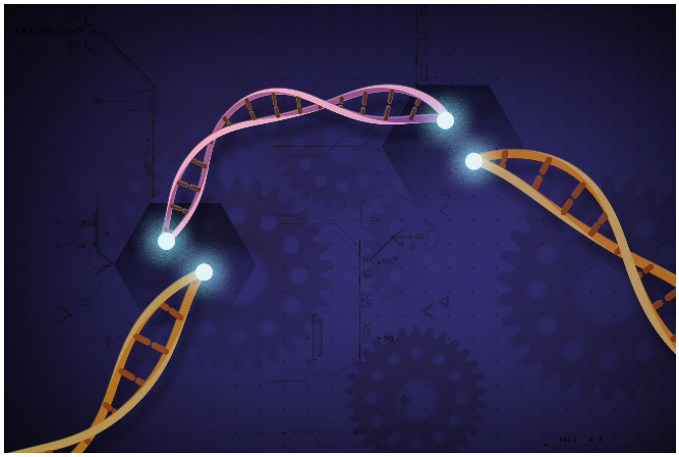

Figure 43. CRISPR-Cas9 is a customizable tool that lets scientists cut and insert small pieces of DNA at precise areas along a DNA strand, allowing scientists to study genes in a specific, targeted way. Credit: Ernesto del Aguila III, NHGRI.

About 50 to 60 percent of hearing loss at birth is due to genetic factors, and treatment options for hereditary deafness are limited. NIDCD-supported researchers developed a novel approach to deliver CRISPR/Cas9 gene-editing complexes into the inner ears of newborn mice that preserved more hair cells and significantly reduced progressive hearing loss.[540] Another form of inherited progressive deafness (DFNA27) may be treated by a small-molecule drug that preserved hearing in mouse models.[541,542] These studies shed light on the molecular mechanisms that underlie certain forms of deafness and present novel

[537] https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies/Nusinersen-Spinraza%C2%AE-%E2%80%93-Spinal-Muscular.
[538] Scoles DR, et al. *Nature* 2017;544(7650):362-6. PMID: 28405024.
[539] Becker LA, et al. *Nature* 2017;544(7650):367-71. PMID: 28405022.
[540] Gao X, et al. *Nature* 2018;553(7687):217-21. PMID: 29258297.
[541] https://www.nidcd.nih.gov/news/2018/novel-drug-therapy-partially-restores-hearing-in-mice.
[542] Nakano Y, et al. *Cell* 2018;174(3):536-48. PMID: 29961578.

strategies that may lead to new and more effective therapies for hearing loss caused by inherited genetic mutations.

Some molecular interventions aim to decrease the levels of a compound or specific cell types contributing to disease, either directly or indirectly. The FX-Learn trial (AFQ056 for Language Learning in Children With Fragile X syndrome) will test whether a blocker of metabotropic glutamate receptor 5 can boost language learning in very young children with Fragile X syndrome who will also undergo intensive language therapy in combination with the drug.[543] The study will also identify biomarkers correlated to developmental outcome measures and assess whether the intervention alters the developmental trajectory of children with Fragile X syndrome, including whether they develop autism.

In 2016, FDA approved cerliponase alfa, an enzyme replacement therapy for patients with ceroid lipofuscinosis 2, who are missing the enzyme tripeptidyl peptidase 1. Without this enzyme, fat and protein byproducts build up in neurons and other cells, causing impaired cell function and neurodegeneration. NINDS and other NIH ICs contributed to the development of this drug by identifying the genetic cause of the disease and carrying out initial studies of the drug's treatment efficacy in animal models.[544] NIH also currently supports research to determine whether enzyme replacement therapy delivered directly to the nervous system may improve neurological symptoms in other similar disorders.

Researchers supported by NICHD and NINDS found that loss of the TSC1 gene, one of the genes that can cause tuberous sclerosis complex, led to increased production of the protein connective tissue growth factor and decreased myelin in the brain in a mouse model.[545] Treatments that subsequently removed some of the excess connective tissue growth factor, such as blocking antibodies or genetic deletion, led to better myelin production. These findings suggest that this pathway is a promising target for future therapies for tuberous sclerosis complex.

In the Phase II Safety, Tolerability and Activity Study of Ibudilast in Subjects with Progressive Multiple Sclerosis (SPRINT-MS), ibudilast was well tolerated and significantly slowed the rate of brain atrophy in patients with MS compared to placebo.[546] This study also explored the possibility of using advanced imaging techniques for detecting neurodegeneration. These imaging techniques may facilitate future studies of progressive MS or other neurodegenerative diseases. SPRINT-MS was conducted within the NeuroNEXT clinical trials network and was a public–private partnership with Medicinova and the National Multiple Sclerosis Society.

Researchers demonstrated that short-term (2-week) treatment with the FDA-approved fibromyalgia treatment pregabalin, which may decrease glutamate (the excitatory neurotransmitter) release, reduced the brain's gray-matter volume in areas associated with pain.[547] Of note, these changes in neuroanatomy

[543] https://projectreporter.nih.gov/project_info_description.cfm?aid=9120161&icde=32552846.
[544] https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies/Cerliponase-alfa-Brineura%C2%AE-%E2%80%93-Ceroid.
[545] Ercan E, et al. *J Exp Med* 2017;214(3):681-97. PMID: 28183733.
[546] Fox RJ, et al. *N Engl J Med* 2018;379(9):846-55. PMID: 30157388.
[547] Puiu T, et al. *Arthritis Rheumatol* 2016;68(6):1511-21. PMID: 26816332.

and function were associated with trends in reduction of "clinical" pain as evidenced by changes in the McGill Pain Questionnaire.

The neuropathology of Alzheimer's disease is complex and presents several molecular targets. NIA-supported investigators have found that senescent cells, which are alive but no longer divide or function, play a role in the neurodegeneration associated with AD/ADRD in mouse models, and that eliminating these cells before they cause damage to neurons appears to preserve cognition.[548] Building on that, researchers confirmed that tau accumulation in the brain, but not amyloid-beta, is correlated with an increase in cell senescence in humans and mice.[549] In addition, treatment of mice with dasatinib and quercetin, two compounds known to remove senescent cells, led to a reduction in tau accumulation, loss of nerve cells, and brain changes associated with dementia. Taken together, these studies provide early evidence for several methods to target senescent cells in AD/ADRD. Senescence is believed to be a common characteristic of aging cells, so interventions that reduce senescence could also affect other conditions associated with aging.

NIH's AMP-AD, which was established to discover novel, clinically relevant therapeutic targets and to develop biomarkers to help validate existing targets,[550] consists of two projects. The Biomarkers Project explores the utility of imaging tau, one of the key pathological markers of AD/ADRD, as well as use of imaging and fluid biomarkers for tracking responsiveness to treatment and disease progression. The Target Discovery and Preclinical Validation Project seeks to shorten the time between discovery of potential drug targets and development of new drugs for AD/ADRD treatment and prevention. The project integrates analysis of large-scale molecular data from human brain samples with network modeling approaches and experimental validation, and enables rapid, broad sharing of data and analytical tools. The AMP-AD Knowledge Portal allows researchers to access and analyze human, cell-based, and animal-model datasets on a scale that would not be possible by individual research teams, academic institutions, or pharmaceutical companies. To date, the knowledge portal has more than 1,300 users and contains contributions from 42 investigators across 22 institutions, representing samples from 36 research studies. In August 2018, AMP-AD launched the Agora platform, an interactive, web-based tool that allows researchers to explore curated genomic analyses from AMP-AD and associated consortia.[551] AMP-AD teams have already nominated more than 100 candidate targets for further exploration.

Surgical Interventions, Implants, and Brain Stimulation

Part of the NIH BRAIN Initiative mission is to develop new technologies that can be applied to link brain function and behavior to bring safe and effective devices and treatments to patients. Progress in surgical interventions, implants, and brain stimulation techniques across a wide swatch of neurological diseases has been made in FY 2016–2018.

[548] Bussian TJ, et al. *Nature* 2018;562(7728):578-82. PMID: 30232451.
[549] Musi N, et al. *Aging Cell* 2018;17(6):e12840. PMID: 30126037.
[550] https://www.nia.nih.gov/research/amp-ad.
[551] https://agora.ampadportal.org/genes.

Surgical interventions to remove affected areas or implant stimulatory devices provide relief to many patients with brain injuries and disorders. Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body. Thymectomy, which is surgical removal of the thymus gland, has been a mainstay in the treatment of myasthenia gravis, but no conclusive evidence of its benefit exists. NINDS-supported researchers conducted a multicenter, randomized clinical trial (RCT) comparing thymectomy plus prednisone to prednisone alone. The trial showed that thymectomy improved clinical outcomes over a 3-year period in patients with nonthymomatous myasthenia gravis.[552]

In the case of stroke, time to intervention is of the essence. The NINDS-funded Endovascular Therapy Following Imaging Evaluation for the Ischemic Stroke (DEFUSE 3) trial demonstrated that brain clots can be physically removed by endovascular thrombectomy up to 16 hours (rather than the currently approved 6 hours) after symptom onset, leading to improved outcomes in selected patients as compared to standard medical therapy.[553]

With current technology, spinal cord injury results in permanent loss of movement and sensation, often because injured nerve cells in the spinal cord cannot regrow. Promoting nerve regeneration has had promising results in rodents, but significant differences between rodents and humans make translating these results to the clinic difficult. At the site of injury in monkeys with spinal cord injury, NICHD-supported researchers implanted a scaffold of chitosan, a bioactive and biodegradable material extracted from crustacean shells, which slowly released a chemical that promoted nerve growth.[554] After a 14-week period, the monkeys recovered some motor and sensory function as assessed by noninvasive methods, including imaging and walking analyses. This study is a significant advance in translating treatments for spinal cord injury from animal models to human clinical studies.

Cochlear implants can restore the sense of hearing in individuals who are deaf or severely hard-of-hearing and who do not benefit from hearing aids. Although the cochlear implant is one of the more groundbreaking biomedical achievements in the last 30 years, residual hearing can be lost as a result of cochlear implantation. In a large clinical study of 200 patients, NIDCD-supported scientists compared surgical approaches and electrode characteristics to determine how to best preserve hearing after cochlear implantation.[555] Electrode arrays without a wire and surgical approaches (round window approach) that leave the cochlea intact were associated with the best rates of hearing preservation. Outcomes of this study will provide surgeons with evidence-based direction on the care and management of their patients who may benefit from a cochlear implant.

[552] Wolfe GI, et al. *N Engl J Med* 2016;375(6):511-22. PMID: 27509100.
[553] Albers GW, et al. *N Engl J Med* 2018;378(8):708-18. PMID: 29364767.
[554] Rao JS, et al. *Proc Natl Acad Sci USA* 2018;115(24):E5595-604. PMID: 29844162.
[555] Wanna GB, et al. *Laryngoscope* 2018;128(2):482-9. PMID: 28643327.

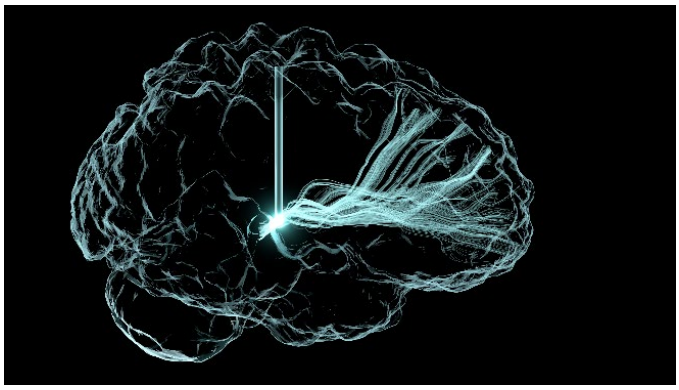

Figure 44. This image is an artistic rendering of deep-brain stimulation, an approach now under clinical investigation to treat cognitive impairment that can arise after a traumatic brain injury and other conditions. The vertical lines represent wire leads with a single electrode that has been inserted deep within the brain. Credit: Andrew Janson, Butson Lab, The University of Utah.

Brain stimulation therapies can play a role in treating hard-to-treat movement and affective disorders. Brain stimulation therapies involve activating or inhibiting the brain directly with electricity. The electricity can be given directly by electrodes implanted in the brain or noninvasively through electrodes placed on the scalp. The electricity can also be induced by using magnetic fields applied to the head. In a study of 20 children and youth with cerebral palsy, researchers supported by NCATS, NIBIB, and NICHD observed that applying an electrical current to the side of the brain unaffected by cerebral palsy resulted in a small, but significant, increase in hand function.[556] The results, achieved with a low and safe level of stimulation, may allow scientists to distinguish those who could benefit from the treatment from those who would not. In a short-term feasibility study, two patients with Parkinson's disease received a deep brain stimulation device programmed to both control symptoms and minimize such adverse effects as dyskinesias or unwanted movements.[557] NIH BRAIN Initiative researchers taught a computer program to recognize a pattern of brain activity associated with dyskinesias, which could then modulate the level of stimulation to decrease symptoms. Future long-term studies are required to determine whether the incidence of dyskinesia is also reduced with this program.

Given the remarkable therapeutic benefits of deep brain stimulation for patients with otherwise treatment-resistant movement and affective disorders, developing noninvasive deep brain stimulation techniques is essential and exciting. Researchers have identified a novel technique for rapid, noninvasive stimulation or inhibition of the hypothalamus using radio waves or magnetic fields to open TRPV ion channels tethered to ferritin nanoparticles.[558] In a separate study, researchers showed that noninvasive temporal interference could be used to selectively stimulate neurons at specific depths.[559,560] For example, mouse hippocampal neurons could be stimulated without affecting the overlying cortex.

[556] Gillick B, et al. *Eur J Paediatr Neurol* 2018;22(3):358-68. PMID: 29456128.
[557] Swann NC, et al. *J Neural Eng* 2018;15(4):046006. PMID: 29741160.
[558] Stanley SA, et al. *Nature* 2016;531(7596):647-50. PMID: 27007848.
[559] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-18-033.html.
[560] Grossman N, et al. *Cell* 2017;169(6):1029-41. PMID: 28575667.

Noninvasive deep brain stimulation techniques may be deployable into human clinical trials, as well as studies of the human brain.

Locked-in syndrome is a state of near-total paralysis that happens as a result of stroke, end-stage neural degeneration, or neuromuscular disease. People with locked-in syndrome have difficulty moving and communicating with others. Brain–computer interface technology uses sensors to measure electrical signals in the brain to run a computer program that can type words when individuals focus on letters on a virtual keyboard. These devices are effective in helping individuals with communication disorders, but users require considerable training and typing is very slow. NIDCD-supported scientists have significantly improved the performance of a brain–computer interface device by developing a program that combines data collected from electrical signals in the brain and from tracking eye movement.[561] Future work will translate this technology from the laboratory into the clinic or home for individuals with locked-in syndrome, potentially helping them communicate more easily and effectively with physicians, caregivers, and family.

Improving Care and Quality of Life

Brain injuries and disorders undoubtedly affect a person's quality of life, as well as that of their caregivers. In fact, the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) program addressed a need in the clinical research community for a tool to measure patient-reported outcomes—such as pain, fatigue, physical functioning, emotional distress, and social role participation—that have a major impact on quality of life across a variety of chronic diseases. Another added layer of complexity to improving quality of life for patients with brain injuries and disorders is that some patients cannot communicate on their own.

For example, other individuals, such as caregivers or proxies, often need to accurately report pain on behalf of individuals who cannot report for themselves. Researchers evaluated the consistency and accuracy of a 12-item pain questionnaire that was modified for use in children with cerebral palsy, with or without cognitive impairment.[562] The questionnaire collected information from the children's caregivers about the children's experiences of pain interference—the degree to which pain interfered with their activities of daily living, such as school and communication. The resulting pain interference scores had strong internal consistency and validity for reporting of children's pain, making this questionnaire a potentially useful tool for researchers and clinicians.

For some individuals with severe speech impairment, communicating is a daily challenge that relies upon use of a computer to generate voice. However, the synthetic voices that are produced are usually a poor representation of a natural human voice, and many people must use the same generic version. To address this problem, NIDCD voice scientists have developed a personalized text-to-speech augmentative and alternative communication device called VocaliD.[563] This device involves blending the speech of two

[561] Kalika D, et al. *J Neural Eng* 2017;14(5):056010. PMID: 28585523.
[562] Barney CC, et al. *Pain Rep* 2018;3(4):e666. PMID: 30123858.
[563] https://www.ted.com/talks/rupal_patel_synthetic_voices_as_unique_as_fingerprints?language=en.

individuals—a donor and a recipient—to recreate the recipient's natural voice. A donor voice is matched with a recipient in terms of gender, age, region of origin, and other characteristics to produce a more personalized synthetic voice. By commercializing VocaliD, NIDCD-funded scientists have refined the technology, automating certain steps and making the entire process of creating personalized, synthetic voices faster and more efficient. These improvements will advance speech synthesis while humanizing machine-mediated spoken interaction for augmentative and alternative communication devices and beyond. Enabling communication is one way to help individuals live productive and fulfilling lives.

To support and improve care for persons with dementia and their caregivers, NIA held or sponsored several workshops. In December 2017, the workshop *State of the Science for Pragmatic Trials of Non-Pharmacological Interventions to Improve Outcomes Among Persons with Dementia and Their Caregivers* was held at NIA.[564] The goals were to review the state of the evidence regarding the effect of interventions to improve care and outcomes for persons with dementia; establish criteria for determining which interventions are ready for launch as pragmatic trials; and consider the infrastructure necessary to conduct, translate, and disseminate such a program of research.

In May 2018, NIA sponsored the *Improving Patient Outcomes through Effective Caregiver-Clinician Communication and Relationships Expert Meeting* in Washington, DC, convened by the National Academies of Sciences, Engineering, and Medicine's Board on Behavioral, Cognitive, and Sensory Sciences.[565] The meeting addressed the role and impact of caregivers in clinical interactions. The purpose of the meeting was to solicit expert views through formal presentations and open discussion on the gaps in knowledge related to how caregiver involvement in clinical settings affects patient–clinician interactions and relationships and, ultimately, the patient's clinical outcomes and well-being.

In addition, NIA released several new funding opportunities to improve care for persons with dementia and their caregivers. Through the Alzheimer's Disease and Alzheimer's Disease Related Dementias Health Care Systems Research Collaboratory, NIA will support a center for collaborative research within and among health and long-term care systems to encourage pragmatic trials of innovative dementia care.[566] The Collaboratory will build investigator capacity, support pragmatic trial design, and maintain the resource and knowledge base for pragmatic trials.

Because the extensive care needs of individuals with Alzheimer's disease typically involve great demands on family members or caregivers, many of these people experience adverse health consequences and economic hardship as a result of lost work and care expenditures.[567] The recent *National Alzheimer's Project Act* recognizes the need to enable family caregivers to continue to provide care while maintaining their own health and well-being. Thus, NIA reissued the program Research on Informal and Formal Caregiving for Alzheimer's Disease, which led to four awards for basic and translational research on

[564] https://nia.nih.gov/sites/default/files/2018-02/pragmatic-trials-summary.pdf.
[565] https://www.nia.nih.gov/sites/default/files/2018-10/2018-05-17%20Improving%20Patient%20Outcomes%20through%20Effective%20Caregiver_Final_10-3-18.pdf.
[566] https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-009.html.
[567] https://grants.nih.gov/grants/guide/pa-files/par-18-179.html.

caregiving for individuals with Alzheimer's disease at the individual, family, community, and population level.

A pair of NIA FOAs encourages small businesses and their research partners to develop assistive robotics and related technology that would enhance health and reduce illness and disability in older Americans suffering from AD/ADRD and other comorbidities.[568,569] For example, grantees are invited to develop robots that function as companions, providing psychosocial support, physiological interventions (e.g., stress reduction through the provision of biofeedback or other forms of behavioral therapy), and assistance with care management and activities of daily living. In addition, these FOAs encourage small businesses and their research partners to develop assistive robotics addressing the needs and conditions of caregivers to older Americans suffering from AD/ADRD.

Depending on the severity of injury, traumatic brain injury can have a lasting impact on quality of life for survivors of all ages. In 2017, NINDS posted a FOA to solicit applications for neurological clinical trials to be carried out in the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN).[570] SIREN provides a robust and readily accessible infrastructure for the implementation of clinical trials in a breadth of emergency indications related to neurology other than stroke, such as status epilepticus, traumatic brain or spinal cord injury, and headache. Successful applicants will collaborate and conduct the trials within the NIH SIREN Network. The trial design should ensure that high-quality, complete data regarding the primary outcome will be collected in the most efficient manner in terms of time, resources, and burden to subjects. Secondary outcomes should be included only when they are anticipated to provide important supportive or explanatory data. The necessity of each secondary endpoint must be justified in light of cost and burden.

Facilitating Research

NIH is home to one of the largest neuroscience research centers in the world. More than 150 laboratories, originating from 11 different ICs, conduct research in the basic, translational, and clinical neurosciences. For example, The Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (IDDRCs) employ advanced technologies to support a broad range of research projects related to intellectual and developmental disabilities.[571] Centers have cores to provide infrastructure support for new research component projects, focusing on comprehensive -omic approaches, multimodal treatment approaches, outcomes measures for interventions or treatments, or public health approaches to intellectual and developmental disabilities. Examples of intellectual and developmental disabilities that the IDDRCs study include chromosomal conditions, such as Prader-Willi, Angelman, Williams, and Down syndromes; X-chromosome disorders, such as Rett and Fragile X syndromes; and disorders that involve

[568] https://grants.nih.gov/grants/guide/pa-files/par-18-185.html.
[569] https://grants.nih.gov/grants/guide/pa-files/par-18-186.html.
[570] https://grants.nih.gov/grants/guide/pa-files/PAR-18-304.html.
[571] https://www.nichd.nih.gov/research/supported/eksiddrc.

biochemical processes and metabolic issues related to brain functioning, such as hypoxia and phenylketonuria.

Through scientific collaboration, pre- and postdoctoral training programs, jointly sponsored seminar series and Special Interest Groups, scientists at NIH contribute to a vital and growing neuroscience research community. This expansive research network supports tissue bank networks and clinical trials. For example, the NIH NeuroBioBank is a network of brain and tissue banks that aim to systematically collect, store, and distribute post-mortem brain and other tissues for research dedicated to the improved understanding, care, and treatment of individuals with developmental, neurological, and movement disorders.[572]

Since 2011, NICHD has led the Down Syndrome Consortium, a public–private collaboration, to foster communication and idea-sharing among NIH, individuals with Down syndrome and their families, and national organizations.[573] The consortium also supports and publicizes DS-Connect®, a web-based health registry that serves as a national health resource for individuals with Down syndrome and their families, researchers, and health care providers.[574] The registry facilitates communication and online resource sharing through a secure, confidential database. With more than 4,200 registrants to date, DS-Connect has allowed 35 researchers to successfully complete recruitment for their studies. In addition, the Cytogenetic and Down Syndrome Models Resource at The Jackson Laboratory, supported by NIA and NICHD, maintains and distributes chromosome aberration stocks that provide mouse models for Down syndrome at reduced cost to researchers across the country, broadening the scope of Down syndrome research.[575]

To optimize the design of clinical trials for rare diseases, which are defined by having fewer than 200,000 patients in the U.S., NINDS has released a FOA to support clinical studies that will seek to validate clinical outcome measures or biomarkers or to characterize cohorts of relevant patients with rare neurological or neuromuscular diseases.[576] Through the support of trial readiness studies, NINDS expects to accelerate the initiation of clinical trials for rare diseases and to increase the likelihood of success in those trials.

Guiding the Field

Considering that NIH is home to one of the largest neuroscience research centers in the world, the 11 different ICs that fund and conduct neuroscience research must work together to identify research priorities and coordinate strategic plans to advance the field of neuroscience for the progress of biomedical research and benefit to public health. Research priorities are identified by convening experts and stakeholders in a particular field.

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[572] https://neurobiobank.nih.gov/.
[573] https://downsyndrome.nih.gov/.
[574] https://dsconnect.nih.gov.
[575] https://www.jax.org/research-and-faculty/resources/cytogenetic-and-down-syndrome-models-resource/models-resource-request-for-animals-form.
[576] https://grants.nih.gov/grants/guide/pa-files/PAR-18-534.html.

In 2016, NINDS and NICHD held the second of two workshops that brought together scientists, clinicians, and advocates for individuals affected by cerebral palsy.[577] Based on workshop discussions, high-priority recommendations were classified into three main areas: basic and translational research, clinical research, and workforce development. The final NINDS and NICHD *Strategic Plan for Cerebral Palsy Research* presented these recommendations as a collective vision for the cerebral palsy research community to advance together over the next 5 to 10 years.

The neurodevelopmental disorders field increasingly recognizes the urgent need to develop and validate biomarkers to enable progress in clinical trials. In December 2017, several NIH ICs—including NCATS NICHD, NIMH, and NINDS—held the *Biomarkers to Enable Therapeutics Development in Neurodevelopmental Disorders Workshop*.[578] The purpose of the workshop was to discuss biomarkers that have the potential to enable clinical trial readiness and translational success in neurodevelopmental disorders associated with autism or intellectual disability.

In 2012, the *National Plan to Address Alzheimer's Disease* was released with five ambitious goals both to prevent future cases of AD/ADRD and to better meet the needs of the millions of American families currently facing this disease.[579] From 2016 to 2018, the field of AD/ADRD held summits and unveiled frameworks and national strategies to achieve the goal to treat and prevent Alzheimer's disease by 2025. To fund this essential work, NIH annually submits to the President and Congress a professional judgment budget that estimates the additional funding, above the base for AD/ADRD, needed to effectively treat and prevent these disorders by 2025.[580] The estimate—often referred to as a bypass budget because it is presented without modification through the traditional federal budget process—also summarizes NIH-funded research and promising research opportunities.

To help achieve the goals outlined in the National Plan, NIA established the Alzheimer's Disease and Alzheimer's Disease Related Dementia Research Implementation Milestone Database to link users to information on initiatives and activities funded by the NIH and other funding organizations.[581] The Alzheimer's Disease-Related Dementias Summit 2016 addressed special research priorities for AD/ADRD, including frontotemporal, Lewy body, mixed, and vascular dementia.[582] Organized by NINDS in collaboration with NIA, the summit is part of the *National Plan to Address Alzheimer's Disease: 2015 Update* and is complementary to *NIA's Alzheimer's Disease Research Summit 2015*.

In April 2018, the NIA and the Alzheimer's Association (AA) unveiled the *NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease*.[583,584] This proposed biological definition is based

[577] https://www.ninds.nih.gov/About-NINDS/Strategic-Plans-Evaluations/Strategic-Plans/2017-NINDS-NICHD-Strategic-Plan-Cerebral-Palsy.
[578] https://meetings.ninds.nih.gov/Home/General/17888.
[579] https://aspe.hhs.gov/national-plans-address-alzheimers-disease.
[580] https://www.nia.nih.gov/about/bypass-budget-proposal-archive.
[581] https://www.nia.nih.gov/research/milestones.
[582] https://www.ninds.nih.gov/News-Events/Events-Proceedings/Events/Alzheimers-Disease-Related-Dementias-Summit-2016.
[583] Jack CR Jr, et al. *Alzheimers Dement* 2018;14(4):535-62. PMID: 29653606.
[584] Silverberg N, et al. *Alzheimers Dement* 2018;14(4):576-8. PMID: 29653608.

on measurable changes in the brain and is expected to facilitate better understanding of the disease process and the sequence of events that lead to cognitive impairment and dementia. The new research framework focuses on biomarkers grouped into different pathologic processes of Alzheimer's disease, which can be measured in living people with imaging technology and analysis of cerebral spinal fluid samples. It also incorporates measures of severity using biomarkers and a grading system for cognitive impairment. The framework will apply to clinical trials and can be used for observational and natural history studies.

In October 2018, NIA released *Together We Make the Difference: National Strategy for Recruitment and Participation in Alzheimer's Disease and Related Dementias Clinical Research,* the culmination of more than 2 years of dedication and work to outline practical, proactive approaches to help study sites engage a wider, more diverse number of volunteers.[585] This National Strategy was developed with facilitation by AA and the expertise and insights from a collaborative network of government, private, academic, and industry stakeholders, as well as from individuals, caregivers, and study participants. The strategy focuses on four large themes:

- Increase awareness and engagement at a broad, national level.
- Build and improve capacity and infrastructure at the study site level.
- Engage local communities and support participants.
- Develop an applied science of recruitment.

As public and private funding agencies around the world enhance and expand their support of AD/ADRD research, coordination of funding strategies and leveraging of resources are urgently needed to maximize the impact on public health, avoid duplication of effort, and reduce inefficiency. In 2018, the International Alzheimer's and Related Dementias Research Portfolio (IADRP) v.2 was released to build on IADRP's initial mission to collate and categorize the portfolios of major organizations for areas of shared priorities, as well as areas of opportunities to inform coordination and collective efforts that seek to advance AD/ADRD research.[586]

Finally, pain is the most common reason for seeking medical care. It is also a common reason people turn to complementary and integrative health approaches. The Federal Pain Research Strategy is an effort of the Interagency Pain Research Coordinating Committee and the NIH Office of Pain Policy to oversee development of a long-term strategic plan to advance the federal pain research agenda.[587] The strategy is relevant to the mission of all federal agencies and departments that support pain research. The research priorities of the Federal Pain Research Strategy are intended to guide strategic research planning and to support funding decisions that will fill crucial gaps in the federal pain research portfolio.

[585] https://www.nia.nih.gov/research/recruitment-strategy.
[586] https://iadrp.nia.nih.gov/.
[587] https://iprcc.nih.gov/Federal-Pain-Research-Strategy/Overview.

Life Stages, Human Development, and Rehabilitation

Research in the areas of life stages, human development, prevention and screening, and rehabilitation works together to improve our ability to protect and promote health by understanding the interplay between health, development, and function throughout the lifespan. That knowledge is then applied to design and deliver effective prevention strategies to decrease the risk of disease and rehabilitation strategies to mitigate the effects of disability. These research areas complement one another and work together to generate knowledge and tools to ensuring that each person lives to their fullest potential.

Summary of NIH Activities

NIH funds research in these areas throughout each of the 27 ICs. In particular, NICHD—which focuses on the needs of children, pregnant women, and people with disabilities—and NIEHS—with a mission to discover how the environment affects people in order to promote healthier lives—contribute to this area. In addition, NIA has pioneered work on aging that has shed light on the effects of earlier life experiences on health in the aging population. Work in prevention and screening within NIH, with partners in federal agencies outside of NIH, and with academic and professional organizations outside of the government is coordinated through the OD's Office of Disease Prevention (ODP).

Human Development

Research on human development seeks to understand organism function and development during the earliest stages of formation from cells, tissues, and organs through gestation and childhood. It includes research aiming to understand both how organisms typically develop and how that development may be affected by environmental exposures.

The immune system is critically important throughout our lives. However, we do not yet have a complete understanding of how it develops. NICHD has issued a program announcement to support studies on the very early development of the immune system, including the cellular communication that exists between the mother and fetus that may shape or influence immune system development and maturation. Findings from these studies may lead to an improved understanding of the mechanisms behind autoimmune diseases.[588]

We are also depending on our fundamental understanding of genetic activity during a critical developmental time as single cells develop into entire bodies. A single fertilized egg develops into many different cell types, tissues, and organs that fit together to create a body. Researchers funded by NICHD used a combination of sensitive nucleic acid sequencing and labeling technologies, together with innovative computational tools, to construct a detailed picture of this process at the level of individual cells. By taking multiple snapshots of the genetic activity within single cells of developing zebrafish and frog embryos, they were able to show how each early cell differentiates into a specific cell type. This

[588] https://grants.nih.gov/grants/guide/pa-files/PAR-18-333.html.

technology was awarded the Science Breakthrough of 2018 by the American Association for the Advancement of Science (AAAS) and was carried out alongside NIMH, NHGRI, NCI, the Howard Hughes Medical Institute, and the Wellcome Trust.[589–591]

In addition to what we typically think of as genetic materials, researchers funded by NIEHS and NIA have also studied telomeres—or the ends of chromosomes (the bundled structures within our cells that are composed of DNA)—and their relationship to health. This growing area of research was the focus of a meeting bringing together experts in fundamental telomere biology, epidemiology, clinical practice, and social sciences to discuss the current state of the field. These experts discussed the ways the status of telomeres can be used to understand exposures and susceptibility in population-based research—for example, as indicators of exposure or susceptibility to disease.[592]

While we know that genes themselves and our genetic material can have profound impacts on our health, research funded by NCATS has also shown that our understanding of the impact of a given set of genes evolves quickly. In a study supported by the University of Texas Southwestern Medical Center Clinical CTSA hub, scientists found that children with epilepsy may benefit from a reinterpretation of prior genetic testing results every 2 years, since consensus standards and guidelines for interpreting hereditary genetic variants are continually evolving. Advances in publicly available databases and standardized interpretation criteria have improved the clinical interpretation of gene variants. Reinterpretation of results every 2 years has been life changing for some epilepsy patients.[593,594]

Environmental exposures can also have a profound effect on development. This is another important and active area of research, which seeks to understand harmful environmental exposures and their effects on health. In order to stimulate research in this area, NIEHS issued a series of FOAs, including a call for multidisciplinary research projects that use a combination of animal/cell models and noninvasive human placenta tissues or biomarkers to investigate how early-life exposures affect placental growth, development, and function, as well as the subsequent health of the offspring.[595] In addition, NIEHS opened a call for grant applications addressing the preconception exposure window and health of the offspring that encourages proposals that use animal models but focus on whether environmental chemical exposures during the time period between preconception (prefertilization) to development of germ cells can be mechanistically linked to later-life outcomes in the first-generation offspring.[596]

This type of research has already yielded insight into key questions of development. In research funded by NIEHS in collaboration with EPA, a model of human prenatal exposure to phthalates simulated in a rat model identified changes in the brain, including reduced numbers of neurons and synapses, reduced size

[589] Farrell JA, et al. *Science* 2018;360(6392). pii: eaar3131. PMID: 29700225.
[590] Briggs JA, et al. *Science* 2018;360(6392). pii: eaar5780. PMID: 29700227.
[591] https://vis.sciencemag.org/breakthrough2018/.
[592] https://www.niehs.nih.gov/news/events/pastmtg/2017/telomeres/index.cfm.
[593] https://www.utsouthwestern.edu/newsroom/articles/year-2018/reanalyzing-gene-tests.html.
[594] SoRelle JA, et al. *JAMA Pediatr* 2018 Nov 5:e182302. PMID: 30398534.
[595] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-17-005.html.
[596] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-16-007.html.

of the medial prefrontal cortex, and a deficit in cognitive function. These results may have serious implications for people because the medial prefrontal cortex is involved in executive function and associated with development of many neuropsychiatric disorders.[597–599]

Using a different model—the *Xenopus laevis* frog model—NIDCR-supported researchers tested the effects of aerosolized e-cigarette liquids. They found that e-cigarette exposure during embryonic development induces a variety of defects, including median facial clefts, midface hypoplasia (incomplete development), cranial cartilage and muscle defects, and a reduction in the blood supply to the face. Furthermore, their findings suggest that although nicotine is not the main factor in inducing craniofacial defects, it can exacerbate the effects of the other e-cigarette liquid components.[600] Researchers funded by NIDCR also examined the *Isthmin 1* gene in the same frog model. Knocking down expression of the gene in *X. laevis* produced animals with mild to severe craniofacial anomalies, including cleft lip/palate (CL/P). This study demonstrates how effectively the findings from basic research can be validated in an animal model system to provide scientists tools to develop treatment interventions.[601]

Addressing craniofacial disorders and syndromes broadly, NIDCR's FaceBase Consortium gathers, organizes, and disseminates data relevant to craniofacial research and funds projects to generate new data and develop innovative technologies. Nearly 600 datasets are available to the scientific community, along with the analytics tools to help researchers query, organize, manage, and use the information. The power of the FaceBase Consortium is its ability to encourage and accelerate both scientific collaborations and new ways of examining and combining datasets to create novel insights into craniofacial development. FaceBase's next phase, announced in 2018, will use existing data to build a comprehensive 3-D facial scan library, which could one day be used as a diagnostic aid in clinical settings to more accurately identify and improve the management and treatment of craniofacial disorders.[602,603]

The joints, or sutures, of the developing skull are a reservoir for mesenchymal stem cells (MSCs) that give rise to bones of the skull. If these MSCs are depleted during development, sutures fuse prematurely, resulting in a craniofacial disorder called craniosynostosis. NIDCR-supported scientists demonstrated that suture MSCs help regulate bone-forming osteoblasts and bone-resorbing osteoclasts to control skull development. Understanding how these different cells interact to regulate bone formation and tissue homeostasis may lead to new approaches to treatment.[604]

Hydrocephalus, or water in the brain, is a condition where excess cerebrospinal fluid builds up in the brain, negatively affecting brain growth and cognitive development in children. It can result from a variety of causes, including congenital abnormalities, brain hemorrhage, or infection. The typical treatment is to

[597] https://www.ncbi.nlm.nih.gov/pubmed/30012688.
[598] https://www.eurekalert.org/pub_releases/2018-07/sfn-pcl071318.php.
[599] Jetten AM. *Cell Mol Life Sci* 2018;75(19):3473-3494. PMIDs: 29779043.
[600] Kennedy AE, et al. *PLoS One* 2017;12(9):e0185729. PMID: 28957438.
[601] Lansdon LA, et al. *Genetics* 2018;208(1):283-296. PMID: 29162626.
[602] https://www.facebase.org/.
[603] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-19-003.html.
[604] Guo Y, et al. *Bone Res* 2018;6:30. PMID: 30345151.

implant a shunt to drain the fluid. However, these shunts will ultimately fail, thus requiring emergency surgery. Researchers funded by FIC and NICHD published results showing that a less invasive hydrocephalus surgical procedure combined with cauterization or burning-off of fluid-producing tissue was shown to be effective and was less prone to subsequent failure.[605,606]

Children with craniofacial disorders often have a range of physical, behavioral, and social challenges, including problems with speech and language, hearing, and facial expressions. NIDCR-funded researchers observed children with craniofacial microsomia, a condition in which the lower part of the face is smaller than normal, to understand how these facial abnormalities change emotion-related facial movements and how this affects changes in hearing, speech, socialization, and behavior. Although older children with craniofacial microsomia often have learning disabilities, infants with craniofacial microsomia did not show developmental or language delays or changes in facial expressiveness.[607,608]

Previous studies have shown that mothers who smoke have an increased risk of bearing a child with CL/P, indicating that smoking is one of the environmental factors that contribute to CL/P. NIDCR-funded scientists have demonstrated that mothers exposed to secondhand smoke are also more likely to have a child with CL/P and that the increased risk was consistent for different populations and types of CL/P. This research emphasizes the importance of identifying maternal environmental risk factors for CL/P to enable the improvement of prenatal prevention strategies. It also emphasizes the importance of studying new forms of nicotine consumption, such as e-cigarettes.[609]

PFAS also have been studied by NIEHS-funded researchers because of their pervasive use in nonstick cookware, stain-resistant fabrics, food packaging, and firefighting foams. Public health concerns regarding PFAS pollution are increasing. The Responsive Evaluation and Assessment of Chemical Toxicity (REACT)-PFAS approach will use chemical-specific studies to evaluate a number of endpoints relevant to children's exposures to PFAS, including developmental toxicity and neurotoxicity, effects on the placenta, changes to human embryonic stem cells, and inhibition of milk protein production.[610] This last area of research is particularly important, because research funded by NINR has shown that human milk consumption improves short- and long-term health outcomes in very low birthweight infants.[611]

A significant challenge lies not only in understanding whether specific exposures affect development and health, but also in identifying what it is to which we might be exposed and how it affects health. The Toxicology in the 21st Century (Tox21) program is a federal collaboration among NIH's NCATS, the National Toxicology Program at NIEHS, EPA, and FDA. Tox21 researchers aim to develop better toxicity assessment methods to quickly and efficiently test whether certain chemical compounds have the potential to disrupt processes in the human body that may lead to negative health effects. In 2016, The

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[605] https://vector.childrenshospital.org/2017/12/shunting-alternative-etv-cpc-hydrocephalus/.
[606] Kulkarni AV, et al. *N Engl J Med* 2017;377(25):2456-2464. PMID: 29262276.
[607] Hammal Z, et al. *Cleft Palate Craniofac J* 2018;55(5):711-720. PMID: 29377723.
[608] Speltz ML, et al. *J Pediatr*. 2018;198:226-233.e3. PMID: 29685618.
[609] Kummet CM, et al. *Am J Epidemiol* 2016;183(9):834-41. PMID: 27045073.
[610] https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2018/june/presentations/10devito_508.pdf.
[611] Johnson TJ, et al. *J Perinatol* 2019;39(1):120-128. PMID: 30341399.

NCATS Tox21 team launched a Transform Toxicity Testing Challenge titled Innovating for Metabolism. Current high-throughput screening (HTS) assays do not fully incorporate chemical metabolism and thus may miss chemicals that are metabolized to a more toxic form in the body. The Challenge calls on innovative thinkers to find new ways to incorporate physiological levels of chemical metabolism into HTS assays, which will help researchers more accurately assess effects of chemicals and better protect human health.[612,613]

Even after exposures and their effects are understood by scientists, yet another challenge remains in disseminating the findings from research. The Children's Environmental Health Network (CEHN) provides training opportunities to childcare providers and licensing agencies with the goal of reducing environmental exposures in childcare settings. CEHN identified Michigan as a target state to conduct these trainings and, in coordination with our Community Advisory Board and their partners, NIH generated a coalition letter to send to the Michigan Department of Education to request that the Office of Great Start partner with CEHN to bring the Eco-Healthy Child Care Train the Trainer session to child care providers in the state of Michigan. CEHN is in conversations with the Michigan Department of Education to explore this opportunity.[614]

Environmental exposures, however, are not limited to chemical exposures. In research funded by NICHD and NIDA, researchers found that limiting screen time and encouraging healthy sleep were associated with better cognition in children. Using data from more than 4,500 children ages 8–11 years old in the first wave of the Adolescent Brain Cognitive Development (ABCD) study, researchers determined that only half of the children studied met the current recommendations for sleep (9–11 hours per day), 37 percent met the screen time recommendation (less than 2 hours), and only 18 percent met the physical activity recommendation (1 hour). Global cognition was positively associated with each additional recommendation met. Children who met all three recommendations, children who met the screen time and sleep recommendations, and children who met only the screen time recommendation had higher cognitive scores than children who met none of the recommendations.[615]

[612] https://archive.epa.gov/epa/newsreleases/federal-agencies-partner-launch-transform-tox-testing-challenge-improve-chemical.html.
[613] https://ntp.niehs.nih.gov/update/2017/11/toxchallenge/index.html.
[614] https://sph.umich.edu/cehc/outreach/index.html.
[615] Walsh JJ, et al. *Lancet Child Adolesc Health* 2018;2(11):783-791. PMID: 30268792.

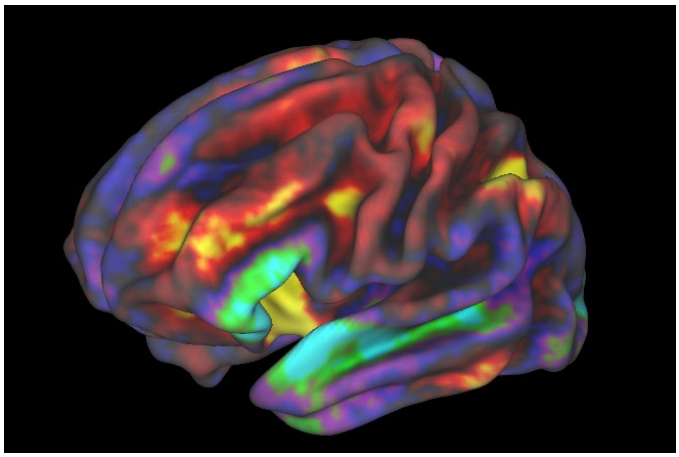

Figure 45. Functional magnetic resonance imaging (fMRI) Image of Preteen Brain from the Adolescent Brain Cognitive Development (ABCD) Study. Credit: Richard Watts, Ph.D., University of Vermont and Fair Neuroimaging Lab, Oregon Health & Science University.

Research on human development also includes the study of developmental disabilities, such as ASD. This area includes research to develop a more complete understanding of the etiology of ASD and improve the diagnosis and quality of life of those living with ASD.

Multiple prenatal/maternal environmental toxins and exposures have been linked to ASD, but the associations of single agents are relatively weak, suggesting it is the combination of multiple maternal exposures that increases vulnerability in offspring. Researchers funded by NIEHS are using a new mouse model that combines the effects of maternal stress and exposure to diesel exhaust, both of which have been implicated in autism, to establish a causal link between prenatal environmental exposures and dysfunction of neural cells critical for normal brain development.[616]

NIMH issued funding opportunities to develop and validate new screening methods for ASD that can be used in infancy. This was in collaboration with other ICs, including NICHD, NIDCD, NIEHS, and NINDS. NIH-funded research has identified risk markers within the first 12 months of age, yet a critical gap exists in translating these methods into practical, efficient, and inexpensive screening tools that could be implemented in the general population and within community settings. Additional efforts focus on improving the accuracy of commonly used autism screening tools, developing and identifying early screening tools for vulnerable populations, translating screening tools into clinical practice, and identifying biomarkers for ASD.[617–619]

As part of their support of the Autism Centers of Excellence network, NIEHS and NICHD have funded the Longitudinal Brain and Behavior Study of Autism from Infancy though School Age program, which is analyzing data on school-age outcomes in infants at familial risk for autism. These infants have been examined using detailed brain imaging and behavior assessments from 3 to 36 months of age in hopes of

[616] https://projectreporter.nih.gov/project_info_details.cfm?aid=9552837&icde=0.
[617] https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-19-120.html.
[618] https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-19-121.html.
[619] https://www.nimh.nih.gov/news/science-news/science-news-about-autism.shtml.

identifying brain and behavior predictors of school-age cognitive, behavioral, and learning problems in high-risk children and characterizing the dynamics of brain development in children with autism from infancy through school age in order to develop timely and effective interventions.[620]

Children with ASD often have difficulties relating to others, including family pets, and often treat pets as inanimate objects. NINR-funded research has shown that therapeutic horseback riding (THR) improved social cognition and communication in children with ASD. This study examines whether THR also affects interactions that ASD children have with their family pets, which can serve to act as therapeutic animals themselves. Scientists assessed the impact of THR in a group of children (ages 6–16) with ASD who had family pets. They found that THR led to improvements in animal attachment scores and animal abuse scores. Further study is needed to determine if THR can also improve interactions between children with ASD and their families.[621]

Individuals with ASD can become overwhelmed in environments with a lot of stimuli, such as dental offices. As a result, ASD children are less likely to receive routine oral care, leading to a greater risk for oral disease. NIDCR-funded scientists are performing a clinical trial testing relatively simple modifications to the dental office environment to make dental clinics more accessible and comfortable and avoid the sensory overload often experienced by children with ASD, thus improving their access to dental care. Building on the success of these modifications, NIDCR is funding the integration of similar strategies to improve access to dental care for children with Down syndrome, since they also experience mental and physical challenges that have implications for oral care. This work is part of the trans-NIH INCLUDE initiative to address critical health and quality-of-life needs for individuals with Down syndrome.[622,623]

Life Stages

Life stages research studies of health concerns at specific stages of life and also seeks to link exposure at earlier stages of life to health outcomes experienced during later stages of life. The exposures considered may range from environmental and industrial contaminants to hormones and developmental experiences and disease. All can have long-ranging effects on human health.

Beginning with research at very early stages of life, the Neonatal Research Network (NRN) is a collaborative network of neonatal intensive care units across the United States, comprising 18 clinical centers and a data coordinating center. The NRN is supported by NICHD with co-funding from other ICs for specific projects. Focused on newborns, particularly extremely low-birth-weight infants, the NRN conducts clinical trials and clinical studies in such areas as sepsis and other infections, bronchopulmonary dysplasia and other lung conditions, and necrotizing enterocolitis, a condition in which the intestines lack oxygen or blood flow.[624]

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[620] https://projectreporter.nih.gov/project_info_details.cfm?aid=9388680.
[621] Petty JD, et al. *Int J Environ Res Public Health* 2017;14(3). pii: E256. PMID: 28273822.
[622] www.projectreporter.nih.gov/project_info_description.cfm?aid=9694299.
[623] https://www.nih.gov/include-project.
[624] https://neonatal.rti.org/.

NICHD also funds work to understand the causes of stillbirth in low- and middle-income countries. Stillbirth rates remain high in resource-limited countries around the world, but current systems for identifying and classifying causes of stillbirth are most accessible to higher-income countries. Most such systems can help with the development of prevention strategies but require such procedures as autopsy and analysis of placental tissue. These procedures are not easily available in resource-limited countries. Instead, a new classification system relying on data that are readily available in low-income countries has been used and has yielded a wealth of clinical data when tested in six countries (Democratic Republic of Congo, Guatemala, India, Kenya, Pakistan, Zambia). In a cohort of more than 100,000 women studied, researchers in NICHD's Global Network found a stillbirth rate of 27.2 percent per 1,000 births. Asphyxia was the cause of nearly half (47 percent of the stillbirths), followed by infection (21 percent), congenital anomalies (8 percent), and preterm birth (7 percent). Other clinical data suggested that the majority of stillbirths may have occurred during labor; therefore, better obstetric care may help prevent these deaths.[625]

Researchers have also found other elements of obstetric care to be critical for infant health. In 2012, the American College of Obstetricians and Gynecologists recommended a 30- to 60-second delay before clamping the umbilical cord to boost blood volume in all preterm deliveries. In 2016, they included this recommendation for term infants. Delaying umbilical cord clamping by 30–60 seconds was shown to be beneficial, though the optimum duration of the delay was not established. To determine whether more than just a 60-second delay in cord clamping is safe without increasing any complications, researchers randomly assigned full-term newborn babies to two groups. In the first group, the cord was clamped immediately, and in the second group, cord clamping was delayed for 5 minutes. In both groups, newborn babies were placed directly on their mother's abdomen after birth. Babies with delayed cord clamping had a higher blood volume and higher levels of hemoglobin (the red blood cell protein that carries oxygen from lungs to tissues). The groups exhibited no differences in the rates of jaundice or symptoms related to hemoglobin levels. These results suggest that delaying cord clamping by up to 5 minutes may have some benefit for full-term infants without posing much risk.[626]

Researchers also considered newborns with particular needs. A 2017 NIDA-funded study showed that buprenorphine is more effective than morphine in treating withdrawal symptoms in newborns prenatally exposed to opioids, known as neonatal abstinence syndrome (NAS). Unlike morphine, buprenorphine did not affect breathing rates, although medications were otherwise comparable for safety. Researchers conducted an RCT comparing sublingual buprenorphine to oral morphine in 63 infants with NAS. Infants had shorter treatment durations and hospital stays when given buprenorphine versus morphine. Breathing rates were reduced among infants receiving morphine compared to buprenorphine, although weight gain, liver function, and heart rate tests showed similar safety profiles for the two medications.[627,628]

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[625] McClure EM, et al. *BJOG* 2018;125(2):131-138. PMID: 28139875.
[626] Mercer JS, et al. *J Perinatol* 2017;37(3):260-264. PMID: 27929530.
[627] https://www.drugabuse.gov/news-events/news-releases/2017/05/study-shows-buprenorphine-more-effective-than-morphine-treatment-opioid-withdrawal-in-newborns.
[628] Kraft WK, et al. *N Engl J Med* 2017;377(10):997-998. PMID: 28877016.

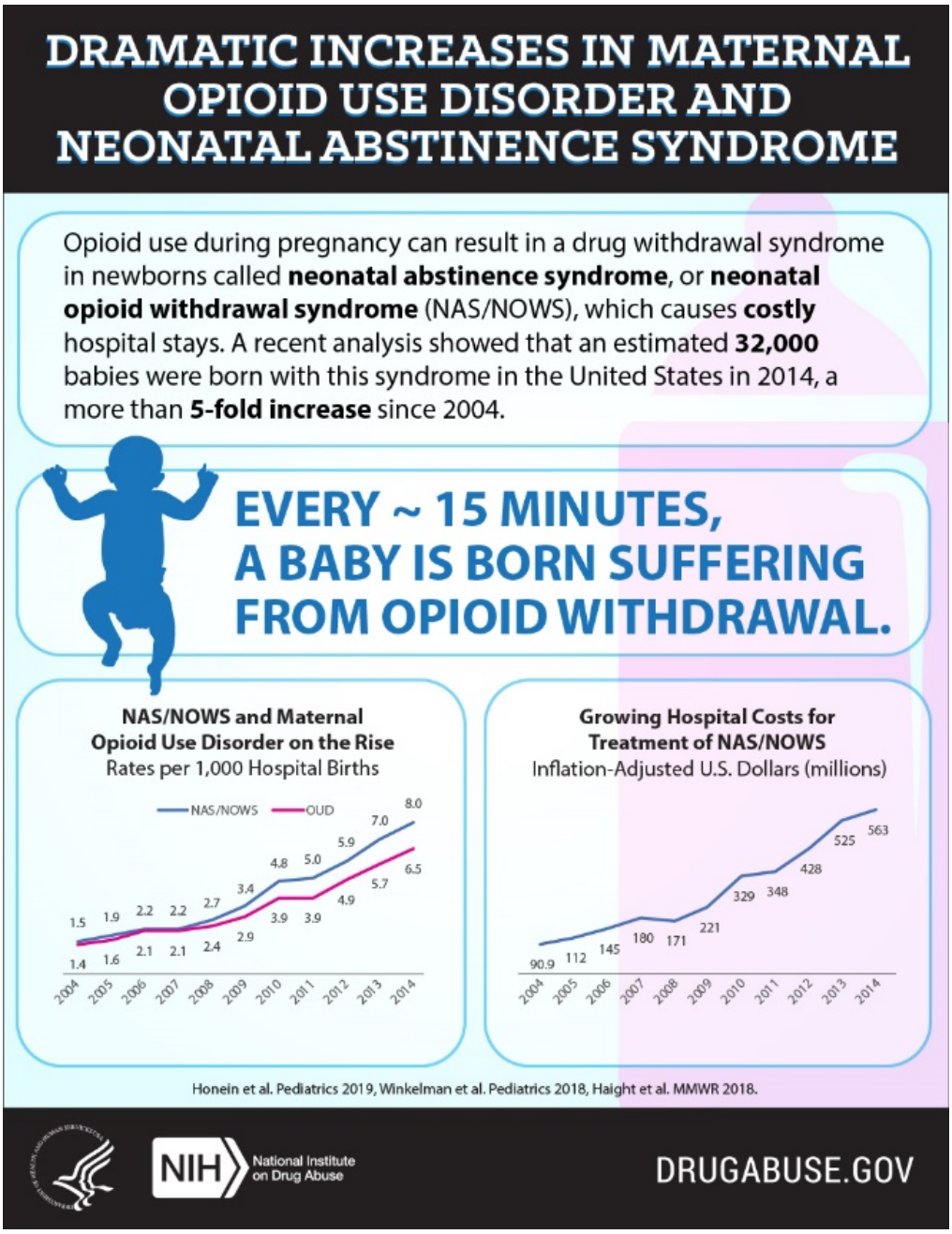

Figure 46. Dramatic Increases in Maternal Opioid Use Disorder and Neonatal Abstinence syndrome": Infographic. Credit: NIDA.

Even among prescribed drugs, those approved for adults may not be safe and effective for children. Yet limited information regarding safety and efficacy may be available regarding use by children, because they are often excluded from clinical studies. To address this, NICHD leads pediatric pharmacology studies under the *Best Pharmaceuticals for Children Act (BPCA)* in partnership with ICs across NIH. *BPCA* aims to identify and sponsor clinical trials for drugs that lack dosing, safety, or efficacy data in children by submitting carefully monitored clinical study data to FDA to modify label information. Research supported by the *BPCA* has resulted in several FDA label changes with updated dosing and efficacy information for children, including a label change for lisinopril for children with kidney transplants and lorazepam for

treating epileptic seizures, as well as a proposed label change for acyclovoir for neonates and infants with herpetic infections.

Other related efforts are also underway, including the Pediatric Trials Network, supported by NICHD, which has completed clinical studies on several drugs, showing effective dosing and safety of rifampin, methadone, and caffeine in neonates.[629] NICHD-funded scientists studied pediatric dosing of the antibiotic solithromycin, which is sometimes used to treat bacterial pneumonia in infants, children, and adolescents. They established dosing information and found that solithromycin was generally well tolerated by pediatric patients. Scientists plan to proceed with a larger clinical trial to ensure the drug is safe and effective for children.[630]

Recognizing that beyond drugs, optimal critical care also differs between children and adults, the NICHD's Collaborative Pediatric Critical Care Research Network (CPCCRN) aims to reduce morbidity and mortality from pediatric critical illness and injury by enhancing knowledge of the scientific bases of pediatric critical care practice. Research topic areas include bereavement and grief, functional outcomes, intensive care clinical processes and protocols, infection, multiple organ dysfunction syndrome, and sepsis.[631]

A Trans-NIH Pediatric Research Consortium (N-PeRC) was established in June 2018 to further develop collaborative opportunities in pediatric research across NIH. N-PeRC aims to harmonize activities across Institutes, explore gaps in the overall pediatric research portfolio, and share best practices to advance science. The consortium meets several times a year to discuss scientific opportunities and potential new areas of collaboration, including efforts to enhance research training for the next generation of pediatricians.[632,633]

The CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect address child maltreatment as a significant public health concern. This program will allow researchers to assess the efficacy and effectiveness trials of child abuse and neglect interventions, examine the long-term impact of specific and understudied types of maltreatment, study the neurobiology of abuse and neglect and implications for health outcomes, and develop screening tools and assessment measures for early identification and treatment of specific types of abuse and neglect.[634]

The reproductive sciences—encompassing reproduction, infertility, and gestation—are also an active area. This period is critical for the development of offspring, as well as for women bearing children. Research in this area includes the period before conception through the period of gestation to the event of a child's birth.

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[629] https://bpca.nichd.nih.gov/.
[630] Gonzalez D, et al. *Antimicrob Agents Chemother* 2018;62(8). pii: e00692-18. PMID: 29891609.
[631] https://www.nichd.nih.gov/research/supported/Pages/cpccrn.aspx.
[632] https://www.nih.gov/news-events/news-releases/new-trans-nih-consortium-aims-advance-pediatric-research-global-level.
[633] https://www.nichd.nih.gov/research/supported/nperc.
[634] https://grants.nih.gov/grants/guide/rfa-files/rfa-hd-18-012.html.

To improve the health and well-being of mothers, their infants, and families and to reduce perinatal morbidity associated with infections, NICHD supports scientific research to increase the understanding of infectious diseases transmitted from mother to child. To that end, in 2018 NICHD reissued a FOA that encourages research studies and trials that improve the understanding, prevention, and clinical outcomes of non-HIV infections that can be transmitted from women to their offspring during pregnancy, labor, delivery, and breastfeeding.[635] High-priority perinatal infections of interest include herpes simplex viruses, viral hepatitis, Chagas disease, and more. Additionally, researchers supported by NICHD and CDC analyzed data from the National Birth Defects Prevention Study and found that maternal cold or flu with fever early in pregnancy was significantly associated with eight birth defects.[636] This NICHD-supported research will hopefully improve the prevention, diagnosis, and treatment of infectious diseases in mothers and their children, as well as inform counseling and treatment for pregnant women.

NICHD's National Centers for Translational Research in Reproduction and Infertility (NCTRI) form a national network of centers that promote multidisciplinary interactions among basic and clinical scientists interested in establishing high-quality translational research programs in the reproductive sciences. The centers also serve as national resources for the training and career development of young scientists electing to pursue careers conducting research in high-priority areas of reproduction and infertility. The centers facilitate and accelerate bidirectional knowledge transfer between the laboratory and clinic, with the goal of improving human reproductive health through enhanced communication, innovation, and research excellence.[637]

NIEHS-funded Investigators from Brigham and Women's Hospital are developing an automated, low-cost tool to predict a woman's ovulation and aid in family planning, in collaboration with other NIH ICs, the American Society for Reproductive Medicine (ASRM), The American College of Obstetricians and Gynecologists (ACOG), and the Society for Reproductive Endocrinology and Infertility (SREI).[638–640] Capitalizing on advancements in several areas—including microfluidics, artificial intelligence, and the ubiquity of smartphones—the team has built an ovulation testing tool that can automatically detect fern patterns—a marker of ovulation—in a saliva sample. The team evaluated the performance of the device using artificial saliva in the lab and validated results in human saliva samples from six subjects, observing greater than 99 percent accuracy in effectively predicting ovulation.[641]

Once ovulation occurs and an ovum is successfully fertilized, the placenta is critical in communication between mother and child. NICHD's ongoing Human Placenta Project, designed to provide information about placental health noninvasively and in real time, is yielding new insights to help researchers further their efforts to improve maternal health and pregnancy outcomes. Since the project launched, NIH has awarded more than $50 million in Human Placenta Project grants. For example, several research studies

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635 https://grants.nih.gov/grants/guide/pa-files/pa-18-092.html.
636 Waller DK, et al. *Birth Defects Res* 2018;110(4):342-351. PMID: 29094488.
637 https://www.nichd.nih.gov/research/supported/NCTRI.
638 https://www.asrm.org/.
639 https://www.acog.org/?IsMobileSet=false.
640 https://www.socrei.org/home?ssopc=1.
641 https://www.brighamandwomens.org/about-bwh/newsroom/press-releases-detail?id=3221.

have now assessed technologies that image the placenta in real time during pregnancy, obtaining data on placental blood flow, oxygen levels, and metabolism. NICHD also launched the Placental Atlas Tool in 2018, a curated dataset that serves as a resource for placental research.[642– 647] The current FOA for this line of research includes Novel Approaches to Safe, Non-Invasive, Real Time Assessment of Human Placenta Development and Function Across Pregnancy.[648]

Placental abruption—the premature separation of the placenta—can lead to devastating complications, including hemorrhagic shock, uterine rupture, and kidney failure during pregnancy. Physical exertion may increase the risk of placental abruption. To understanding this more definitively, scientists supported by NICHD interviewed 663 women with placental abruption at seven hospitals in Peru, where they asked women about physical exertion in the prior week and in the hour before they experienced symptoms. The researchers found that episodes of moderate or heavy physical exertion were associated with an immediately heightened risk of placental abruption in the subsequent hour, compared with periods of lower exertion or rest. The risk of placental abruption within an hour of moderate or heavy physical exertion was lower among women who habitually engaged in physical activity more than three times a week prior to pregnancy. Because physical activity during pregnancy is also associated with lower risks of gestational diabetes, preeclampsia, blood clots, and cesarean delivery, the researchers pointed out that it is important for women who are pregnant to remain active at levels that are safe for them.[649]

PregSource® is a research project that aims to improve understanding of pregnancy by gathering information directly from pregnant women via confidential online questionnaires. Led by NICHD in collaboration with NCCIH, NHLBI, NIEHS, NIMHD, NINR, OBSSR, and ORWH within NIH and various professional society and charitable partners, the project is gathering information directly from pregnant women about what they feel, think, do, and experience during pregnancy and after giving birth to provide more insights on pregnancy and how to improve care.[650]

In response to a mandate in the *21st Century Cures Act*, an HHS Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was established, with representatives from NIH and a number of government, academic, and industry partners.[651,652] Although understanding differences in biological processes or the effects of different exposures during pregnancy and lactation is crucial, research to test the safety and effectiveness of medications typically does not include pregnant and lactating women. Led by NICHD, the PRGLAG Task Force reported in September 2018 to the Secretary and

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642 https://www.nichd.nih.gov/research/supported/HPP/default.
643 https://pat.nichd.nih.gov/.
644 Hwuang E, et al. *J Magn Reson Imaging* 2019;49(1):59-68. PMID: 30390347.
645 Krishnamurthy U, et al. *J Magn Reson Imaging* 2018;48(1):283-289. PMID: 29274251.
646 Hirsch AJ, et al. *Nat Commun* 2018;9(1):263. PMID: 29343712.
647 Markovic S, et al. *Proc Natl Acad Sci USA* 2018;115(10):E2429-E2436. PMID: 29444856.
648 https://grants.nih.gov/grants/guide/pa-files/PAR-18-884.html.
649 Chahal HS, et al. *Am J Epidemiol* 2018;187(10):2073-2079. PMID: 29992226.
650 https://pregsource.nih.gov/.
651 *21st Century Cures Act* (P.L. 114-255). Available here: https://www.congress.gov/bill/114th-congress/house-bill/6.
652 https://www.nichd.nih.gov/About/Advisory/PRGLAC.

Congress on the state of the science and research gaps that need to be filled in order to inform the use of both pharmaceuticals and dietary supplements by pregnant and lactating women. In addition to reporting extensive research gaps with regard to safety, efficacy, and dosing with regard to medications that are widely used for clinical management of both pregnancy-related and other disorders in pregnant and lactating women, the Task Force found a dearth of safety, efficacy and dosing data specifically for the unique physiology and other characteristics of these populations. Among the Task Force recommendations was more, better, and more timely research. A number of FOAs have been issued by NICHD that promote the need for more information on how medications are processed during pregnancy and lactation.[653–655]

This research is critically important, because many factors influence pharmacology during both normal and abnormal pregnancies. In related efforts, the NICHD's Obstetric-Fetal Pharmacology Research Centers (OPRC) Network provides the expert infrastructure needed to test therapeutic drugs during pregnancy, allowing researchers to conduct safe, technically sophisticated, and complex studies that will help clinicians protect women's health, improve birth outcomes, and reduce infant mortality. Recent publications include investigations on the effects of antidepressants during pregnancy and the safety of medication to prevent preeclampsia.[656–658]

The NICHD's Maternal-Fetal Medicine Units Network is designed to conduct rigorous clinical trials in maternal-fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. The aims of the Network are to reduce maternal, fetal, and infant morbidity related to preterm birth, fetal growth abnormalities, and maternal complications and to provide the rationale for evidence-based, cost-effective obstetric practice. Current projects include RCTs of preventing obstetrical hemorrhage after cesarean delivery, preventing effects from cytomegalovirus infection, and treating sleep apnea in pregnancy. Completed projects include RCTs on monitoring fetal heart rate, preventing preterm birth, and preventing preeclampsia.[659]

In a retrospective study of births at an academic medical center between 2005 and 2012, researchers examined more than 3,000 low-risk, full-term births by first-time mothers. First-time mothers were found to have more unplanned cesarean sections and labor interventions—including oxytocin use, regional anesthesia use, and delivery with the use of forceps or vacuum—when treated by an obstetrician versus a nurse-midwife. Understanding the differences in labor management style between different groups of clinicians is essential to helping lower cesarean rates among first-time, low-risk mothers and improve outcomes for the mothers and their offspring.[660]

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[653] https://grants.nih.gov/grants/guide/pa-files/PAR-13-389.html.
[654] https://grants.nih.gov/grants/guide/pa-files/par-18-215.html.
[655] https://grants.nih.gov/grants/guide/pa-files/par-18-506.html.
[656] https://www.nichd.nih.gov/research/supported/opru_network.
[657] Constantine MM, et al. *Am J Obstet Gynecol* 2016;214(6):720.e1-720.e17. PMID: 26723196.
[658] Avram MJ, et al. *Clin Pharmacol Ther* 2016;100(1):31-3. PMID: 27037844.
[659] https://www.nichd.nih.gov/research/supported/mfmu.
[660] Carlson NS, et al. *Birth* 2018;45(2):159-168. PMID: 29388247.

Even after giving birth, a woman is at risk for complications. A woman's highest risk for postpartum stroke occurs in the first 10 days that she is home from the hospital, according to a new analysis of a very large, nationally representative database of hospital discharge and readmission records. However, hospital records also indicated that 80 percent of postpartum patients who were readmitted with pregnancy-associated acute stroke had not been diagnosed with hypertension during pregnancy, nor had they had preexisting hypertension when they became pregnant. The patients with stroke were older than 39 years of age and had longer hospital stays, cesarean delivery, pre-pregnancy diabetes, tobacco use, and Medicaid coverage. The NICHD- and NINDS-supported researchers studied this and found that although postpartum stroke is relatively rare, prompt and optimal maternal blood pressure management in the first days after hospital discharge following birth is critical.[661]

At NIH, ORWH coordinates research activities and events specific to women—including, but not limited to, reproductive health. In 2016, ORWH sponsored the publication of the summary of a convened workshop examining the health of U.S. women in the context of a multitude of factors that influence health. Consensus from the workshop emphasized the concern that many analyses of health data are not stratified by sex or gender, making it difficult to understand fully the relevance of research findings to the health of women.[662]

Further expanding on this, ORWH published a manuscript reviewing major sex differences in heart disease and discussing areas of cardiology research in which women have been underrepresented. Additionally, the authors emphasize the importance of factoring sex as a biological variable into the design, analysis, and reporting of preclinical research, because this research critically informs the design and execution of clinical trials.[663]

To address some of the challenges that exist in reframing research to include consideration of sex, ORWH also supports an additional mechanism by which research on women can be expanded. An administrative supplement is a noncompeting award that provides additional funding to a currently funded grant to meet increased costs that are within the scope of the approved project. ORWH provides one year of support to ongoing NIH-funded grants to catalyze exploratory research on sex and gender differences. The program bolsters the research of NIH IC grantees to encourage sex and/or gender comparisons in preclinical and clinical studies and encourages researchers to study females and males as a catalyst for considering sex as a fundamental biological variable in research.[664]

NIH has also funded research to understand the needs and challenges for both men and women as they age. For example, acupuncture, as practiced in clinical settings, may significantly improve menopause-related symptoms. For example, NCCIH-funded researchers found that acupuncture significantly reduced vasomotor symptoms—by as much as 36.7 percent—and improved several quality-of-life measures, such

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[661] Too G, et al. *Obstet Gynecol* 2018;131(1):70-78. PMID: 29215510.
[662] The National Academies, Committee on Population, Division of Behavioral and Social Sciences and Education. *Improving the Health of Women in the United States: Workshop Summary.* 2016. http://sites.nationalacademies.org/DBASSE/CPOP/DBASSE_171620.
[663] Clayton JA, et al. *Clin Cardiol* 2018;41(2):179-184. PMID: 29480590.
[664] https://orwh.od.nih.gov/research/funded-research/administrative-supplements.

as hot flash interference, sleep quality, physical symptoms, memory symptoms, and anxiety. All these benefits persisted at least 6 months beyond the end of acupuncture treatment. The researchers also gained insights about dosing; they began to see significant benefits after three acupuncture treatments, and they saw maximum clinical benefits after a mean of eight treatments.[665]

As men age, many have testosterone levels well below those found in healthy younger men. In most cases, these low levels are not due to diseases known to affect testosterone levels, such as testicular or pituitary conditions. However, many of these men have symptoms that could be related to low testosterone, including diminished sexual function, decreased mobility, and fatigue. The NIA-supported Testosterone Trial was the first to enroll large numbers of men with low serum T levels to test the effects of one year of testosterone therapy on numerous outcomes important to older men. Investigators found that, compared to placebo, testosterone treatment for one year improved mood and sexual function, but not cognition. Treatment increased hemoglobin levels in men with anemia and improved volumetric bone mass density and estimated bone strength, particularly in the spine. Testosterone treatment did increase coronary artery plaque volume, but further research is needed to determine the clinical significance of this finding.[666– 671]

In efforts to understand aging at a fundamental level, NIA-supported investigators analyzed biomarker data collected from almost 5,000 participants in the Long Life Family Study, an international project studying families that include members who have reached a very old age in good health. Blood biomarkers—including standard hematological measures, lipid biomarkers, and markers of inflammation and frailty—were measured in participants ranging in age from 30 to 110 years and were correlated with changes in physiological functions over time, as well as with risk of cancer, cardiovascular disease, type 2 diabetes, and mortality. The investigators identified a set of markers in blood that can predict survival, better physical function, disease-free aging, dementia, and cardiovascular disease. The identified biomarker signature could potentially become a potent diagnostic and prognostic tool for studies on medical interventions to prevent or delay age-related diseases.[672]

Despite the growing evidence that physiological changes in early life can influence health and disease across the adult years, development and aging continue to be studied separately. Little is known about the relationships between developmental processes earlier in life and how they influence aging and changes that contribute to age-related diseases and health conditions. NIA is soliciting research to identify potential juvenile protective factors, experimental studies to test hypotheses about their effects on aging,

[665] Avis NE, et al. *Menopause* 2016;23(6):626-37. PMID: 27023860.
[666] https://clinicaltrials.gov/ct2/show/NCT00799617.
[667] Snyder PJ, et al. *N Engl J Med* 2016;374(7):611-24. PMID: 26886521.
[668] Budoff MJ, et al. *JAMA* 2017;317(7):708-716. PMID: 28241355.
[669] Resnick SM, et al. *JAMA* 2017;317(7):717-727. PMID: 28241356.
[670] Snyder PJ, et al. *JAMA Intern Med* 2017;177(4):471-479. PMID: 28241231.
[671] Roy CN, et al. *JAMA Intern Med* 2017;177(4):480-490. PMID: 28241237.
[672] Sebastiani P, et al. *Aging Cell* 2017;16(2):329-338. PMID: 28058805.

and translational studies to explore the potential risks and benefits of maintaining or modulating the levels of juvenile protective factors across the adult years.[673,674]

Ultimately, declining independence and the use of multiple medications can negatively affect the quality of life of older adults. Specifically examining oral health, scientists are evaluating a partner-assisted oral care program designed to help elderly dementia patients improve and maintain oral hygiene and positive oral health behaviors. This research is being done through a partnership between NIDCR and the NIH Initiative on Alzheimer's Disease and Related Disorders. Researchers are assessing the overall effectiveness of the program, including changes in oral health communication, knowledge, and self-efficacy for participants and care partners.[675]

In general, certain oral health conditions—such as dry mouth, caries, and periodontitis—are associated with aging, as are other chronic physical and cognitive impairments that can contribute to reduced oral health in older adults. As older adults make up a rapidly growing segment of our population, NIDCR launched the Interdisciplinary Collaborations to Promote Research in Oral Health and Aging initiative to develop innovative approaches that enhance oral health and well-being of older adults. The first phase of this initiative encouraged research on the biology of aging in dental, oral, and craniofacial tissues as they relate to parallel processes in other tissues and organs.[676,677]

As we age, individuals are more likely to have more than one chronic medical condition. To better understand multimorbidity, NCI, NIA, NIMHD, OBSSR, and ODP convened the workshop *Measuring Multimorbidity: Matching the Instrument and the Purpose* in fall 2018. The idea for the workshop arose from the ODP-sponsored trans-NIH Prevention Scientific Interest Group on Comorbidity. The workshop's purposes were to (a) identify the best available instruments for measuring multimorbidity and characterize their validity, reliability, and ease of use; (b) propose a set of recommendations that would facilitate adoption of particular tools and methods for specific purposes; and (c) identify areas of research needs and gaps to improve measurement of multimorbidity.[678]

Not to be neglected, people serve as caregivers for family members at different phases of their life. The impact and science of caregiving is thus an area of investment for NIH, as well. An RCT was funded by NINR and conducted in four states, with more than 300 grandmothers who were the primary caregivers for their grandchildren, with the goal of improving parenting skills, limiting custodial grandparents' psychological distress, and improving the psychological well-being of the custodial grandchildren. The trial tested a behavioral parent training intervention and a cognitive-behavioral training intervention, comparing both to a control group receiving information only, and found that both behavioral parent training and cognitive-behavioral training had positive effects as measured by an improvement in

[673] https://grants.nih.gov/grants/guide/pa-files/par-17-126.html.
[674] https://grants.nih.gov/grants/guide/pa-files/par-17-127.html.
[675] www.projectreporter.nih.gov/project_info_description.cfm?aid=9438210.
[676] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-18-009.html.
[677] https://grants.nih.gov/grants/guide/rfa-files/rfa-de-18-010.html.
[678] Salive M. *Inn in Aging* 2018;2(S1):607.

parenting practices and reduced psychological distress in the custodial grandmothers and improved psychological well-being in their grandchildren.[679]

In summer 2017, NINR and partners presented a summit titled *The Science of Caregiving: Bringing Voices Together*. The Summit provided perspectives across the spectrum of caregiving, including the importance of caregiving across the lifespan, as well as current and future directions for research to improve the health of patients and caregivers. The summit brought together an audience of researchers, advocates, health care providers, educators, and others interested in the science of caregiving.[680]

Research in the area of prevention and screening aims to limit the impact of disease and disability by reducing the risk of disease or by detecting disease at an early stage so that its effects can be minimized. Prevention aims to ensure that disease does not occur, and screening efforts aim to detect disease and address it as early as possible to minimize its effects. More information about research in prevention and screening for specific diseases, such as cancer and cardiovascular disease, is contained in the sections corresponding to those diseases.

The ODP provides leadership for the development, coordination, and implementation of prevention research in collaboration with NIH ICOs. Leveraging machine-learning technology to identify prevention research, ODP was able to provide the first detailed analysis of the NIH prevention research portfolio for primary and secondary prevention research in humans and related methods research.[681]

In 2018, ODP released the *ODP Strategic Plan FY 2019–2023, Prevention Research: Building a Healthier Future*, which includes six strategic priorities that will guide the activities of the Office over the next 5 years. The priorities are interconnected, allowing each area to leverage staff expertise and build upon prevention-related resources, tools, and initiatives developed across the ODP. In addition to the six strategic priorities, the plan includes three crosscutting themes, which represent areas of opportunity for the ODP to serve as a catalyst for developing, coordinating, and implementing new activities to better integrate disease prevention into trans-NIH initiatives. The crosscutting themes address health disparities, leading causes and risk factors for premature morbidity and mortality, and dissemination and implementation research.[682]

ODP also works closely with federal agency partners, as well as relevant academic and professional societies. For example, with participation from nearly all ICOs across NIH, ODP leads the NIH Prevention Research Coordinating Committee (PRCC), which serves as a venue for exchanging information on recent scientific advances in disease prevention. The PRCC also examines the impact of new policies on research, plans new initiatives and discusses ongoing initiatives, and highlights program accomplishments. As a trans-NIH, trans-agency committee, the PRCC provides a broad perspective on the current state of the

[679] Smith GC, et al. *J Fam Psychol*. 2018;32(6):816-827. PMID: 30188171.
[680] https://www.ninr.nih.gov/sites/files/docs/Caregiving-Summit-Summary-508c.pdf.
[681] Murray DM, et al. *Am J Prev Med* 2018;55(6):915-925. PMID: 30458950.
[682] https://prevention.nih.gov/about-odp/strategic-plan-2019-2023.

science and actively disseminates information about prevention-related activities sponsored by both federal and non-federal organizations to NIH ICOs.[683]

The Healthy People Initiative provides science-based national goals and objectives with 10-year targets designed to guide national health promotion and disease prevention efforts to improve the health of all Americans. As part of its mission, Healthy People has established benchmarks and monitored progress over three decades in order to (1) engage multiple sectors to strengthen policies and improve practices that are driven by the best available evidence and (2) increase public awareness of the determinants of health, disease, and disability and the opportunities for progress. The ODP provides advice on Healthy People activities, and ODP staff serve on the Federal Interagency Workgroup, the principal advisory body for the development of the Healthy People initiative.[684]

The U.S. Preventive Services Task Force (USPSTF) is an independent panel of non-federal experts in prevention and evidence-based medicine and is composed of primary care providers.[685] The USPSTF conducts scientific evidence reviews of a broad range of clinical preventive health care services (such as screening, counseling, and preventive medications) and develops recommendations for primary care clinicians and health systems that are published in the form of Recommendation Statements. AHRQ has been authorized by Congress to convene the Task Force and to provide ongoing scientific, administrative, and dissemination support to the Task Force. ODP works closely with AHRQ and the USPSTF to provide scientific input from NIH ICs on draft research plans, draft evidence reviews, and clinical practice guidelines to be included in the *Guide to Clinical Preventive Services*.

ODP also disseminates information to NIH ICs about high-priority evidence gaps for clinical preventive services that have been identified by the USPSTF. In order to coordinate these activities, ODP designed a new, web-based *USPSTF Annual I Statement Reporting Survey* to obtain more comprehensive information from NIH ICOs related to Insufficient Evidence statements (I statements) released by the Task Force. Information from the survey highlights NIH activities relevant to the USPSTF I statements, providing an opportunity for ICs to consider whether their current and planned activities are sufficient or what additional activity may be warranted to better inform the development of USPSTF clinical guideline recommendations. A summary of the survey results was shared with NIH ICOs, AHRQ, and the USPSTF.[686]

The Community Preventive Services Task Force (CPSTF) is an independent, non-federal panel of prevention experts that conducts rigorous systematic reviews and provides public health recommendations to CDC to inform decision-making about policy, practice, and research priorities for community preventive services. Recommendations from the CPSTF are published in *The Guide to Community Preventive Services*. ODP represents NIH as an official liaison member and works with CDC and CPSTF members to ensure that recommendations represent the views, concerns, and needs of NIH and

[683] https://prevention.nih.gov/prevention-research/prcc.
[684] https://www.healthypeople.gov/.
[685] http://www.uspreventiveservicestaskforce.org/.
[686] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/i-statements.

its constituents. ODP staff also serve on or recommend NIH scientists to serve on systematic review teams and help translate CPSTF recommendations into actions.[687]

ODP developed and updated several new webpages to provide information, tools, and other resources to assist a variety of stakeholders in promoting and sharing research in D&I. A new *Research Highlight* was developed to feature D&I prevention research activities, scientific advances, and resources from NIH and other federal partners. The *Prevention Research Articles* section now contains a selection of recent, peer-reviewed articles on D&I research. The *Evidence-Based Programs and Practices* section identifies several databases and other resources that provide information to community planners and implementers, health care and public health professionals, policymakers, and researchers to promote public health using evidence-based strategies. ODP also collaborated with the trans-NIH D&I Working Group to create a new *Resources for Researchers* section on D&I research for the ODP website. The material includes examples and links to funded projects; training opportunities; frameworks, theories, and models; and D&I-related programs, offices, and divisions at NIH. The section also provides information on D&I research FOAs across all ICOs.[688]

Prevention and screening also encompasses screening for genetic disorders at or prior to birth, as well as preventive measures to reduce the risk of disease—these include such measures as physical activity and improvement in diet.

Figure 47. Newborn screening. Credit: NHGRI

NICHD supports the Hunter Kelly Newborn Screening Research Program, which focuses on identifying, developing, and testing newborn screening technologies to improve existing tests, develop new tests, and test interventions for conditions that can be detected through screening. The Newborn Screening Translational Research Network provides resources and infrastructure for researchers studying newborn

[687] https://www.thecommunityguide.org/task-force/about-community-preventive-services-task-force.
[688] https://prevention.nih.gov/research-priorities/dissemination-implementation.

screening. Recent newborn screening developments include a diagnostic assay that allows faster and more inexpensive newborn screening for cystic fibrosis, a bile-based newborn screen for Niemann-Pick disease type C, biomarkers for a rare genetic disorder called medium-chain acyl-coenzyme A dehydrogenase deficiency in newborn blood spots, quicker diagnosis of propionic acidemia, and FDA approval for a device that can detect lysosomal storage disorders. The Secretary of HHS accepted the recommendation of the Advisory Committee on Heritable Disorders in Newborns and Children[689] to add spinal muscular atrophy to the *Recommended Uniform Screening Panel*, a list of disorders for states to consider to screen for as part of their state universal newborn screening programs.[690,691,692,693,694,695] For all of these conditions, NLM has worked with NICHD and other federal partners and state newborn screening programs to update guidance for electronic reporting of newborn screening results using nationally accepted vocabulary and electronic messaging standards.[696–698]

Researchers at NHGRI reported that noninvasive prenatal screening of all 24 chromosomes can detect genetic disorders that may explain miscarriage and abnormalities during pregnancy. Noninvasive prenatal screening involves sampling fetal and maternal DNA extracted from a sample of maternal blood. Typical genomic tests performed during pregnancy have targeted extra copies of chromosomes 13, 18, and 21, but rarely evaluated all 24 chromosomes.[699,700] The findings may ultimately improve the accuracy of these tests, including by explaining why some give false-positive results.

The Newborn Sequencing in Genome Medicine and Public Health (NSIGHT) Program is a joint effort between NHGRI and NICHD to explore the feasibility, benefits, and challenges of incorporating genome sequencing into clinical care during the newborn period. One grantee in this consortium is applying genome sequencing to diagnose acutely ill infants in the neonatal intensive care unit and has found that this approach can decrease infant morbidity by allowing earlier intervention.[701] This group set a Guinness World Record in 2018 for the fastest genetic diagnosis (19.5 hours). Also in 2018, the NSIGHT consortium and Hastings Center issued a special report, which concluded that although sequencing the genomes of some newborns might be appropriate under certain circumstances, not all newborns should receive genome sequencing.[702]

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[689] https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html.
[690] https://www.nichd.nih.gov/health/topics/newborn.
[691] https://www.nichd.nih.gov/news/releases/Pages/sbir_ma_020617.aspx.
[692] Holm IA, et al. *BMC Pediatr* 2018;18(1):225. PMID: 29986673.
[693] Lefterova MI, et al. *J Mol Diagn* 2016;18(2):267-82. PMID: 26847993.
[694] Jiang X, et al. *Sci Transl Med* 2016;8(337):337ra63. PMID: 27147587.
[695] McCrory NM, et al. *J Pediatr* 2017;180:200-205.e8. PMID: 27776753.
[696] https://newbornscreeningcodes.nlm.nih.gov/.
[697] https://cde.nlm.nih.gov/cde/search?q=newborn&selectedOrg=NLM&classification=Newborn%20Screening.
[698] https://loinc.org/newborn-screening/.
[699] Pertile MD, et al. *Sci Transl Med* 2017 Aug 30;9(405). pii: eaan1240. PMID: 28855395.
[700] https://www.genome.gov/27569418/2017-news-relase-sequencing-all-24-human-chromosomes-uncovers-rare-disorders/.
[701] Farnaes L, et al. *NPJ Genom Med* 2018;3:10. PMID: 29644095.
[702] The Hastings Center. *The Ethics of Sequencing Newborns: Reflections and Recommendations*. 2018. https://onlinelibrary.wiley.com/toc/1552146x/2018/48/S2.

Figure 48. Prenatal genome sequencing. Credit: Ernesto del Aguila III, NHGRI.

For adults, screening can also identify those at high risk for subsequent development of health conditions. Screening is a common part of clinical practice and an area in which the USPSTF has identified a number of research gaps. ODP coordinates the activities of a Prevention Scientific Interest Group (SIG) focused on adult screening. This trans-NIH SIG serves as a forum for discussing research interests, activities, and needs/gaps in this area. As a result, the Adult Screening SIG developed a collaborative trans-NIH FOA titled *Increasing Uptake of Evidence-Based Screening in Diverse Adult Populations*.[703] The FOA—issued with participation by NCI, NIA, NIAAA, NIDA, NIDCR, NIMH, NIMHD—is intended to encourage investigations to better understand causes for and develop innovative strategies to reduce disparities in the uptake of evidence-based screening. Research supported by this initiative will enhance the screening process: (1) in diverse populations; (2) in diverse clinical and community settings; and (3) with traditional, nontraditional, and allied health care providers.

Prevention through interventions addressing nutrition and physical activity is also part of this area of research. The 2018 Physical Activity Guidelines Advisory Committee submitted its Scientific Report to the Secretary of Health and Human Services in February 2018. The report summarizes the scientific evidence on physical activity and health and was used by the government to develop the second edition of the *Physical Activity Guidelines for Americans* released by the Surgeon General in November 2018. The HHS Office of Disease Prevention and Health Promotion coordinates the overall effort for this activity. ODP and NCI served as liaisons to the Advisory Committee and helped develop the guidelines.[704]

Go4Life, a partnership between NIA and various federal partners, is an evidence-based exercise and physical activity campaign developed at NIA and designed to help older adults fit exercise and physical activity into their daily lives. Go4Life offers exercises, motivational tips, and free resources to help older individuals get ready, start exercising, and keep going. The Go4Life campaign includes an exercise guide in both English and Spanish, an exercise video, an interactive website, and a national outreach campaign.

[703] https://grants.nih.gov/grants/guide/pa-files/PA-18-932.html.
[704] https://health.gov/our-work/physical-activity/current-guidelines.

Since 2016, NIA has reinvigorated its partnerships and established September as National Go4Life Month.[705]

Prevention research also includes studies to understand the mechanisms by which preventive and protective measures impact disease and disease risk. The SCORE program is a signature ORWH program. Since its inception, the program has been sponsored through partnership with several NIH ICs. SCORE's objective is to expedite the development and application of new knowledge to human diseases that affect women, to learn more about the etiology of these diseases, and to foster improved approaches to treatment and prevention.[706]

Although aspirin is a well-established therapy for the secondary prevention of cardiovascular events, its role in the primary prevention of cardiovascular disease—and other age-related conditions, such as dementia and cancer—is unclear. NIA-supported investigators with the multinational ASPirin in Reducing Events in the Elderly (ASPREE) trial recently reported that in healthy older adults (ages 65 and older without previous cardiovascular events), aspirin did not prolong healthy, independent life free of dementia or persistent physical disability. In addition, the study did not address the effect of aspirin in people younger than age 65. The risk of dying from a range of causes, including cancer and heart disease, varied depending on characteristics of the participants, and further analysis and follow-up of participants will be required to better understand this.[707–710] The investigators emphasized that older adults should continue to follow the advice of their own physicians about daily aspirin use and that the new findings do not apply to people with a proven indication for aspirin, such as stroke, heart attack, or other cardiovascular disease. Further follow-up and analysis of these results are planned.

In 2016, the NIH Common Fund launched the Molecular Transducers of Physical Activity (MoTrPAC). This program allows researchers to develop a comprehensive map of the molecular changes that occur in response to physical activity. Seven clinical sites across the country are recruiting adults and children from diverse racial and ethnic groups to examine how molecular signals are altered following changes in exercise patterns. Additionally, this program is supporting chemical analysis sites, physical activity studies in animal models, a coordination center, and the dissemination of tools and data to the entire biomedical research community.[711,712]

[705] https://www.nia.nih.gov/health/exercise-physical-activity.
[706] https://orwh.od.nih.gov/research/funded-research-and-programs/specialized-centers-research-sex-differences-score.
[707] https://aspree.org/usa.
[708] McNeil JJ, et al. *N Engl J Med* 2018;379(16):1519-1528. PMID: 30221595.
[709] McNeil JJ, et al. *N Engl J Med* 2018;379(16):1499-1508. PMID: 30221596.
[710] McNeil JJ, et al. *N Engl J Med* 2018;379(16):1509-1518. PMID: 30221597.
[711] https://www.nih.gov/news-events/news-releases/nih-awards-aim-understand-molecular-changes-during-physical-activity.
[712] https://www.commonfund.nih.gov/MolecularTransducers.

Rehabilitation

Rehabilitation research includes research to develop treatments for or to better address all types of disability. This includes research in the development of tissues, medicines, devices, or assistive technology addressing physical disability, as well as research addressing social, psychological, or economic effects of trauma.

NICHD- and NINR-funded researchers conducted studies to address sleep disorders in the context of medical rehabilitation. Patients with many different disabilities report problems sleeping, but specific sleep disorders are often not diagnosed. Because sleep affects many physiological and behavioral parameters—depression, anxiety, pain, cancer, cardiovascular changes, immune function—sleep disorders should be diagnosed and appropriately treated to maximize benefit of rehabilitation. Two FOAs have been issued calling for research on how to best approach this complexity in the context of medical rehabilitation for a primary, non-sleep disorder.[713,714]

Researchers also found that patient-directed music helps to control anxiety for patients receiving respiratory support. In an NINR-funded study, an intervention of patient-directed music was found to significantly reduce anxiety and lowered intensive care unit costs by more than $2,000 per patient versus usual care. This finding is significant, in that it demonstrates a cost-effective alternative to pharmacologic interventions for reducing anxiety in mechanically ventilated patients.[715]

NICHD's National Center for Medical Rehabilitation Research (NCMRR) fosters research and research training to enhance the health, independence, and quality of life of people with disabilities. NCMRR has supported technologies for individuals with physical disabilities, such as tools that can help children with cerebral palsy or individuals recovering from stroke to recover limb function. Another example is a skateboard-like device coupled with wearable sensors, which aids infants in crawling. NCMRR's rehabilitation research investments continue to be guided by the 2016 comprehensive *NIH Research Plan on Rehabilitation*, developed with stakeholders across NIH and other federal agencies, as well as researchers and representatives of individuals with disabilities and practitioners.[716–718]

Researchers at NIH's Clinical Center developed a pediatric robotic exoskeleton to treat crouch (or flexed-knee) gait, one of the most debilitating pathologies in children with cerebral palsy. The exoskeleton works differently than previously developed robotics; motion of the user's limbs is tracked in real time and short bursts of assistance are provided at precise times during the walking cycle. In a pilot study, improvements in knee extension with the exoskeleton were similar to or greater than previously reported values for invasive surgery. Importantly, these improvements accrued over the course of the multi-week study,

[713] https://grants.nih.gov/grants/guide/pa-files/par-18-212.html.
[714] https://grants.nih.gov/grants/guide/pa-files/par-17-163.html.
[715] Chlan LL, et al. *Crit Care Med* 2018;46(9):1430-1435. PMID: 29727366.
[716] https://www.nichd.nih.gov/about/org/ncmrr.
[717] NICHD. *Research Plan on Rehabilitation: Moving the Field Forward.* 2016. https://www.nichd.nih.gov/sites/default/files/publications/pubs/Documents/NIH_ResearchPlan_Rehabilitation.pdf.
[718] https://projectreporter.nih.gov/project_info_description.cfm?aid=8121435&icde=42396927.

providing the first evidence to support the use of wearable exoskeletons as a gait rehabilitation strategy for children with cerebral palsy.[719– 723]

Two NICHD-funded rehabilitation technologies received medical device clearance from FDA. One device, which gives an amputee greater control and movement of his/her prosthetic limb, uses pattern-recognition technology to strengthen and improve the analysis of electric signals in the remaining muscles. The second technology, a virtual occupational therapy assistant, helps stroke survivors and others with neurological impairments manage daily tasks. The virtual assistant reacquaints patients with activities that once may have been routine, such as cooking, cleaning, and shopping.[724]

In addition, hearing health is also an active area of research for NIH-funded researchers. Approximately 15 percent of American adults, or 37.5 million people, report some degree of hearing loss. For many of these individuals, assistive technologies, such as hearing aids, could significantly improve their quality of life, yet only about one in four of those who could benefit from hearing aids has ever used them. To help address this important public health issue, NIDCD joined NIA, CDC, FDA, DoD, VA, and the Hearing Loss Association of America to cosponsor a consensus study on accessibility and affordability of hearing health care by the National Academies of Sciences, Engineering, and Medicine.[725,726]

Another area of active research is in the area of regenerative medicine. This area includes research on synthetic biomaterials, stem cells, and tissue engineering.

Müller glia cells, which help keep neurons in the light-sensitive retina healthy, are now also thought to be a possible source of stem cells. NEI-funded researchers recently found that Müller glia—which normally do not divide in the adult retina—could re-enter the cell cycle after Müller glia cells were introduced to another copy of the *beta-catenin* gene by gene therapy in a mammalian model of congenital blindness. They found these Müller glia cells could begin to act as retinal stem cells once more and even divide to form new photoreceptor cells.[727] After an injury, zebrafish, unlike mammals, readily regenerate retinal neurons—another critical element to vision. A key difference between mammals and zebrafish lies in access to DNA by the transcription factor Ascl1. In mammals, reduced accessibility inhibits neuronal regeneration. When Ascl1 is overexpressed in combination with another drug capable of reactivating inert genes, however, NEI-funded researchers were able to regenerate retinal neurons following an injury.[728] In combination, these methods may provide future treatments for retinal injury, thereby restoring vision to the blind.

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[719] https://clinicalcenter.nih.gov/rmd/fab/neuralinterfacing.html.
[720] Lerner ZF, et al. *Sci Transl Med* 2017;9(404). pii: eaam9145. PMID: 28835518.
[721] Lerner ZF, et al. *Sci Rep* 2017;7(1):13512. PMID: 29044202.
[722] Lerner ZF, et al. *IEEE Trans Neural Syst Rehabil Eng* 2017;25(6):650-659. PMID: 27479974.
[723] Bulea TC, et al. *IEEE Int Conf Rehabil Robot* 2017;2017:1087-1093. PMID: 28813966.
[724] https://www.nichd.nih.gov/news/releases/Pages/051517-rehabtech.aspx.
[725] https://www.nidcd.nih.gov/research/hearing-health-care-research-projects.
[726] http://nationalacademies.org/hmd/reports/2016/Hearing-Health-Care-for-Adults.aspx.
[727] Yao K at al. *Nature* 2018;560(7719):484-488. PMID: 30111842.
[728] Jorstad NL, et al. *Nature* 2017;548(7665):103-107. PMID: 28746305.

NIBIB- and NIDCR-supported bioengineers also grew living bone for facial reconstruction. Replacing bone structure from deformities in the head and face can be quite challenging. Current methods involve metal and bone putty obtained from deceased donors or grafted bone from elsewhere within a person's own body. The new method was tested on pigs by using cow bone matrix—what is left over from cow bone after the cells within the structure were removed. Using precise imaging technology, this matrix was shaped to fit into the pigs' jaw-bone area and then seeded with stem cells harvested from the pigs' fat tissues. After three weeks, the matrix was implanted into the pigs. During the 6 months for which the pigs were monitored, the transplanted bone was shown to tolerate forces needed for pigs to chew. [729,730]

NIDCR-funded scientists synthesized an adhesive patch that can be cut to any size and can be used to repair or reconstruct soft tissues and bone. The researchers tested their adhesive on several animal tissues, including skin, cartilage, artery, and liver, even using it to patch a hole in an artificially beating pig heart that was then able to withstand thousands of inflations and deflations. This new adhesive could be used in various dental, oral, and craniofacial procedures, including repairing traumatic injuries or cleft lip and/or palate and improving wound closure and healing while decreasing the risk of infection and scarring.[731]

Research supported by the NIH Common Fund's Regenerative Medicine Program aided in the development of a clinical-grade stem cell line manufactured by coaxing umbilical cord blood cells back into a state in which they have the potential to develop into any cell type in the body. Meeting clinical-grade guidelines is very time-intensive and costly; providing access to clinical-grade stem cells removes a significant barrier to developing cell-based therapies to accelerate discoveries for Alzheimer's disease, spinal cord injury, muscular dystrophy, and many other debilitating diseases.[732]

Chronic Diseases and Organ Systems

A chronic disease is defined as any condition lasting more than 1 year that requires ongoing medical attention, limits a person's daily living activities, or both. Chronic diseases are the leading cause of death and disability in the U.S. Nearly half (approximately 45 percent, or 133 million) of all Americans suffer from at least one chronic disease, and the number is growing. In fact, in the U.S., 6 in 10 adults have a chronic disease, and 4 in 10 adults have two or more.[733] There are many different categories of chronic disease. Some are fatal: 7 of the top 10 causes of death in the U.S. involved chronic diseases;[734] and 13 percent of Americans are disabled or have had their activities limited because of chronic diseases.[735] Furthermore, a recent analysis indicates that treatment of the seven most common chronic diseases,

[729] https://www.nibib.nih.gov/news-events/newsroom/bioengineers-grow-living-bone-facial-reconstruction.
[730] Bhumiratana S, et al. *Sci Transl Med* 2016;8(343):343ra83. PMID: 27306665.
[731] Li J, et al. *Science* 2017;357(6349):378-381. PMID: 28751604.
[732] https://www.nih.gov/news-events/manufactured-stem-cells-advance-clinical-research.
[733] https://www.cdc.gov/chronicdisease/about/index.htm.
[734] https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.
[735] https://www.census.gov/newsroom/facts-for-features/2020/disabilities-act.html.

coupled with productivity losses, will cost the U.S. economy more than $1 trillion dollars annually.[736] However, modest reductions in unhealthy behaviors could prevent or delay 40 million cases of chronic illness per year.[737,738]

Americans are not alone in suffering from chronic diseases. Many chronic diseases and conditions that are common in the U.S.—such as type 2 diabetes, obesity, and heart disease—have a substantial impact on global morbidity and mortality.[739] By 2030, it is anticipated that chronic diseases will account for half the disease burden in low-income countries and more than three-quarters in middle-income countries. Already, chronic diseases account for more than 85 percent of the disease burden in high-income nations.[740]

A multitude of contributors exist for the onset and development of chronic diseases. Some are behavioral, such as drug use (e.g., tobacco, excessive alcohol, other drugs), low levels of physical activity, prolonged sedentary behaviors (which may impair health despite physical activity at other times), and poor eating habits. Others are environmental, involving exposure to toxins and other external factors, particularly for individuals with a higher genetic risk of disease. These long-term diseases affect people of all ages, both rich and poor, in every ethnic group. Furthermore, age plays a factor in the development and worsening of such chronic conditions as hearing loss, chronic kidney disease, vision loss, and osteoarthritis; genetics, which can cause chronic diseases at birth (e.g., sickle cell anemia, hemophilia) and throughout development (e.g., asthma, allergies), also play a role. NIH's long-term efforts to understand, treat, and prevent chronic diseases are helping to reduce the global burden of these conditions.

Summary of NIH Activities

Nearly all NIH ICs support research into chronic diseases. From understanding the molecular and cellular mechanisms behind human health to clinical applications and behavioral interventions to improve quality of life and reduce disease burden, NIH invests heavily in the area of chronic disease research. This section highlights some of the key areas in which NIH is conducting critical research.

Appendix I includes NIH funding for different chronic diseases and organ systems in FY 2016, 2017, and 2018.

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[736] Warers H and Graf M. The Costs of Chronic Disease In The U.S. *Milken Institute.* August 2018. https://www.milkeninstitute.org/sites/default/files/reports-pdf/ChronicDiseases-HighRes-FINAL_0.pdf.
[737] Warers H and Graf M. The Costs of Chronic Disease In The U.S. *Milken Institute.* August 2018. https://www.milkeninstitute.org/sites/default/files/reports-pdf/ChronicDiseases-HighRes-FINAL_0.pdf.
[738] Raghupathi W and Raghupathi V. An Empirical Study of Chronic Diseases in the United States: A Visual Analytics Approach to Public Health. *Int J Environ Res Public Health.* 2018 Mar; 15(3): 431. PMID: 29494555.
[739] Hajat C and Stein E. *Prev Med Rep* 2018; 12: 284-93. PMID: 30406006.
[740] Quam L, et al. *Lancet* 2006;368(9543):1221-3. PMID: 17027712.

Asthma

Asthma, a chronic lung disease that inflames and narrows the airways, causes recurring periods of wheezing (a whistling sound when you breathe), chest tightness, shortness of breath, and coughing. It affects more than 25 million Americans, including more than 6 million children age 18 and under.[741] Asthma is the leading cause of missed school days for children, as well as a driver of preventable hospitalizations and emergency department (ED) visits. NIH supports targeted research aimed at improving the understanding of asthma, its causes, and how asthma can be prevented and treated in both children and adults.

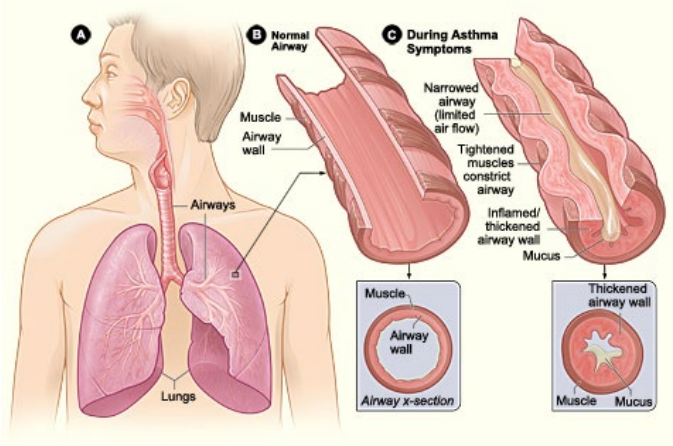

Figure 49. Asthma illustration. A shows the location of the lungs and airways in the body. B shows a cross-section of a normal airway. C shows a cross-section of an airway during asthma symptoms. Credit: NHLBI.

Understanding Prevalence, Risk Factors, and Underlying Biology

NIAID-funded research focuses on reducing the burden of allergy and asthma through studies on causation, prevention, and treatment.[742] Inner-City Asthma Consortium (ICAC) researchers recently found that children who are exposed to mouse, cat, or cockroach allergens during infancy have a lower risk of developing asthma by the age of 7.[743] By contrast, ICAC researchers found that older children who already have asthma and were exposed to airborne mouse allergens at school had increased asthma symptoms and reduced lung function. These studies can inform prevention strategies to lower the risk of developing asthma and treatment strategies to ameliorate symptoms in children with established disease.

NHLBI-funded researchers shed light on the mechanisms of asthma by showing that allergens can trigger inflammatory cells known as neutrophils (a type of white blood cell) to form neutrophil extracellular traps (NETs).[744] Neutrophils use NETs to trap and kill pathogenic bacteria, but the study found that generating

[741] https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm.
[742] https://www.niaid.nih.gov/news-events/exposure-pet-and-pest-allergens-during-infancy-linked-reduced-asthma-risk.
[743] O'Connor GT, et al. *J Allergy Clin Immunol* 2018;141(4):1468-75. PMID: 28939248.
[744] Drake MG, et al. *Sci Transl Med* 2018;10(457). pii: eaar8477. PMID: 30185653.

NETs can cause neutrophils to release most of their vital components and leave behind empty cellular husks, which, in turn, can trigger inflammation.

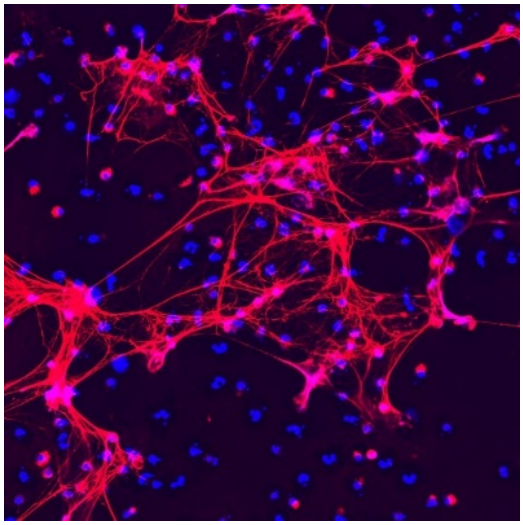

Figure 50. Neutrophil extracellular traps (NETs) are web-like structures that immune cells called neutrophils use to ensnare and kill microbes, such as bacteria or fungi. NETs are shown as DNA (blue) forming a complex with the granule protein neutrophil elastase (red). Credit: Mariana Kaplan M.D., NIAMS

Mucus buildup in the lungs contributes to many lung diseases, but its role in severe asthma is not clear. NIH-funded researchers used a noninvasive imaging technique, called multidetector computed tomography (a CT scan for the lungs) to measure mucus in the lungs. They found that mucus plugs were common in patients with asthma, but not in those without, and that mucus congestion was highest in patients with severe asthma and the poorest lung function.[745] This finding suggests that lung CT of mucus congestion could be used to assess asthma severity and that more effective drugs to clear mucus might help in chronic severe asthma.

Severe Asthma Research Program (SARP) studies the pathobiology of severe asthma and how it differs from mild to moderate asthma at the molecular, cellular, and clinical levels over time.[746] A 2017 SARP study identified several factors associated with exacerbation-prone asthma, including high levels of white blood cells called eosinophils, high body mass index, and responsiveness to bronchodilator medications.[747] The results of the study suggest that exacerbation-prone asthma could be identified with distinctive clinical characteristics and that this may lead to tailored prevention strategies for patients.[748] Another SARP study found evidence of increased pruning of the pulmonary vasculature in patients with severe asthma as compared with those with mild to moderate asthma or normal controls.[749] Higher pruning was associated with reduced lung function, increased exacerbations, and increased markers of

[745] Dunican EM, et al. *J Clin Invest* 2018;128(3):997-1009. PMID: 29400693.
[746] http://www.severeasthma.org/.
[747] Denlinger LC, et al. *Am J Respir Crit Care Med* 2017;195(3):302-13. PMID: 27556234.
[748] https://www.nhlbi.nih.gov/news/2017/director-nhlbi-division-lung-diseases-available-discuss-latest-asthma-research-findings.
[749] Ash SY, et al. *Am J Respir Crit Care Med* 2018;198(1):39-50. PMID: 29672122.

inflammation. This may implicate the pulmonary vascular system, not just the airways, in certain types of severe asthma, providing a rationale for exploring new disease pathways and therapeutic directions.

The NIEHS Clinical Research Unit is continuing research on the Natural History of Asthma with Longitudinal Environmental Sampling (NHALES) study.[750] NHALES will help scientists understand how the environment affects asthma symptoms. NIEHS scientists will examine how bacteria living in and on humans and in their homes, known collectively as the microbiome, may be associated with asthma activity. This 5-year study will provide free treatment, medications, and compensation so participants can get their asthma under control.

An NHLBI-supported trial in a nationwide clinical research network, AsthmaNet, identified differences in the bronchial microbiome—bacteria found in the airways—when comparing healthy people, those with allergies but no asthma, and those with mild asthma. In people with asthma, the makeup of the bronchial microbiome before treatment differed between people who responded to inhaled steroid medications and those who did not respond.[751] Moreover, inhaled steroids further altered the microbiome in responders. Further research in this area may help identify patients most likely to respond to different existing treatments, as well as lead to novel treatments to target specific airway bacteria.

NIEHS intramural researchers are continuing their work on early-life development of lung disease and potential epigenetic underpinnings of asthma. One outcome of this work has been the formation of the Pregnancy and Childhood Epigenetics Consortium (PACE). The results of this study identify many places in the genome that are altered as a result of maternal smoking in pregnancy. For example, the first PACE publication combined data on maternal smoking and DNA methylation in offspring from 16 cohorts and identified 6,000 differentially methylated CpG sites (CpGs) in newborns, half of them novel and many persisting into childhood.[752] These results provide insights into mechanisms underlying the effects of this important exposure.

An NHLBI-funded clinical trial in children aged 1 to 5 years old with asthma requiring daily treatment found that assessing sensitivity to airborne pollutants and a blood test to check the levels of eosinophils (white blood cells that often suggest an allergic reaction) helped identify those children with the best responses to inhaled corticosteroids.[753] Such testing could help balance the expected benefits of steroid treatment with risks, such as the potential for stunted growth.

Additionally, researchers supported by NIEHS model ambient air quality and examined the relationship between particulate matter smaller than 2.5 µm in diameter ($PM_{2.5}$) concentration and asthma, bronchitis, chronic sinusitis, otitis media, pneumonia, and upper respiratory infections in the U.S. state of Georgia. They found that a 10-µg/m^3 increase in same-day $PM_{2.5}$ concentrations was associated with ED visits for children living in a metropolitan area.[754] The study evaluated more than 200,000 children between 2002

[750] https://www.niehs.nih.gov/research/clinical/studies/nhales/index.cfm.
[751] Durack J, et al. *J Allergy Clin Immunol* 2017;140(1):63-75. PMID: 27838347.
[752] Joubert BR, et al. *Am J Hum Genet* 2016;98(4):680-96. PMID: 27040690.
[753] Fitzpatrick AM, et al. *J Allergy Clin Immunol* 2016;138(6):1608-18.e12. PMID: 27777180.
[754] Strickland MJ, et al. *Environ Health Perspect* 2016;124(5):690-6. PMID: 26452298.

and 2010. These results suggest that pediatric ED visits for asthma, wheeze, and upper-respiratory infections are associated with $PM_{2.5}$ concentrations.

Asthma and obesity often occur together in children, but it is unclear whether asthma contributes to the childhood obesity epidemic. Research supported by NIEHS found that children with asthma are 51 percent more likely to become obese over the next decade than children who did not have a respiratory condition.[755] This suggests that children with asthma may be at higher risk of obesity. However, another NIEHS-supported study found that children who used asthma inhalers when they had an attack were 43 percent less likely to become obese.[756] These findings support the evidence of health benefits possible from efforts to improve air quality, particularly among children.

The B-Well-Mom Study aims to increase understanding of factors that predict poor asthma control during pregnancy and basic immunology of pregnancy.[757] Asthma affects about 9 out of 100 pregnant women, with one-third of all pregnant women experiencing worsening symptoms, whereas one-third improve. This multicenter prospective cohort study, supported by NICHD, aims to recruit 500 women in their first trimester of pregnancy and follow them through 4 months postpartum, with the follow-up visits expected to finish in 2019.

The Consortium of Safe Labor,[758] supported by NICHD, collected detailed information from electronic medical records in 228,562 deliveries from 19 hospitals across the U.S. Matching these records with data on daily measures of air quality and pollutants has linked air pollution with a higher risk of preterm birth for mothers with asthma.[759]

Although asthma is common among pregnant women, drugs (uterotonics) used to induce labor contractions or treat severe postpartum bleeding, as well as beta-blocker drugs for high blood pressure control, may make asthma worse. To assess use of these drugs in pregnant women with asthma, NICHD-supported researchers analyzed data on more than 5.6 million women who were hospitalized for delivery complicated by postpartum hemorrhage or preeclampsia. They found that patients with asthma were less likely than those without asthma to have been treated with common uterotonic drugs; however, the beta-blocker drug labetalol was more likely to have been administered by intravenous (IV) therapy to asthmatic women compared with non-asthmatic patients.[760] Clinical guidelines recommend against beta-blockers for patients with asthma; therefore, other effective blood pressure medications could be used in pregnant and postpartum patients with asthma, instead of labetalol.

In the MothertoBaby pregnancy studies (2006–2014), researchers surveyed pregnant women with asthma and rheumatoid arthritis about their medications and compared the resulting data with the women's medical records. The most common medications used during pregnancy were albuterol for asthma and

[755] Chen Z, et al. *Am J Respir Crit Care Med* 2017;195(9):1181-8. PMID: 28103443.
[756] Berhane K, et al. *JAMA* 2016;315(14):1491-501. PMID: 27115265.
[757] https://www.nichd.nih.gov/about/org/diphr/officebranch/eb/B-well-mom.
[758] https://www.nichd.nih.gov/about/org/diphr/officebranch/eb/safe-labor.
[759] Mendola P, et al. *J Allergy Clin Immunol* 2016;138(2):432-40.e5. PMID: 26944405.
[760] Booker WA, et al. *Obstet Gynecol* 2018;132(1):185-92. PMID: 29889742.

prednisone for rheumatoid arthritis. For both conditions, there was low agreement between prescription medication use reported by women and that captured in the medical records, with the women typically reporting more medications than were captured in the medical record.[761] The results suggest that studies of medication use in pregnancy that rely on medical records may underestimate prescription drug use, especially for medications that are not used continuously.

Improving Treatment and Prevention

NHLBI is supporting updates to the 2007 national guidelines for asthma care and has supported completion of rigorous systematic evidence reviews addressing critical issues in asthma diagnosis and management.[762] NHLBI has also established a federal advisory committee that will chart the path for translating new evidence into improved care guidelines for people who have asthma.

An ongoing NHLBI program supports the development and evaluation of Asthma Care Implementation Programs (ACIP) to improve outcomes for children in communities with especially high rates of childhood asthma.[763] Each ACIP consists of interventions targeting four different areas that influence the health of children with asthma: medical care, family, the home, and the community. The ACIPs are testing intervention trials in Providence, Rhode Island; Richmond, Virginia; Philadelphia, Pennsylvania; and three Navajo communities in Arizona. This research is expected to reveal effective programs for addressing asthma disparities that can then be implemented in diverse communities across the country.[764]

Racial disparities are clear among children with asthma. While Black children with asthma are known to have poor outcomes compared with White children, little is known about disparities in preventive asthma care. NHLBI-funded investigators evaluated how frequently providers delivered guideline-based asthma care to Black and White children (ages 2–12 years) with persistent asthma during an office visit, with an assessment of asthma morbidity prior to the visit and again at 2 months follow-up. Prior to the visit, Black children had greater symptom severity and were less likely than White children to report having a preventive medication.[765] These disparities persisted after the office visit. Further efforts to promote consistent guideline-based preventive asthma care are critical to reducing the disparate burden of persistent asthma in Black children.

Non-Hispanic Black children with asthma are more likely to be at high risk for poor outcomes in managing their asthma, often leading to higher rates of treatment in EDs. A study found that allergen exposure and living in poorer areas are associated with more ED visits, as well as ED use in the past year, number of medications used for asthma control, and mold sensitization.[766] Understanding how different population

[761] Palmsten K, et al. *Paediatr Perinat Epidemiol* 2018;32(1):68-77. PMID: 28971498.
[762] Mensah GA, et al. *J Allergy Clin Immunol* 2018;142(3):744-8. PMID: 30036600.
[763] https://www.nhlbi.nih.gov/news/2018/new-grants-will-tackle-childhood-asthma-disparities-risk-communities-0.
[764] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-001.html.
[765] Lewis P, et al. *J Community Health* 2014;39(4):706-11. PMID: 24435717.
[766] Franklin JM, et al. *Ann Allergy Asthma Immunol* 2017;119(2):129-36. PMID: 28479192.

groups experience asthma is key to developing techniques to improve asthma control and ways to limit allergen exposure.

In FY 2017, NHLBI funded 10 clinical centers and one coordinating center as part of the Precision Interventions for Severe and Exacerbation Prone Asthma (PrecISE) Network, which conducts early-phase clinical trials of interventions for severe and exacerbation-prone asthma.[767] Through fine-grained analyses of asthma symptoms and biomarkers in each participant, the researchers will attempt to target interventions to distinct asthma subtypes. They will use a sequential, adaptive trial design to continuously analyze data as they are collected and to add new biomarkers as they are discovered.

At early signs of asthma flare-ups, physicians commonly prescribe large short-term increases in inhaled corticosteroids, but this approach had not been rigorously tested for its benefits in children with asthma.[768] An NHLBI-funded clinical trial of 254 children between 5 and 11 years old found that increasing the dose of inhaled corticosteroids fivefold for 1 week did not prevent severe flare-ups and may affect a child's growth.[769]

The Vitamin D Antenatal Asthma Reduction Trial (VDAART), supported by NHLBI, was the first trial in the U.S. to look at interventions in pregnant women as a way to prevent asthma in their children. The study involved 881 pregnant women considered to be at high risk for having a child with asthma. Half of the women received a supplement containing 4,000 international units (IU) of vitamin D, and the other half were given a placebo. All participants were also given a standard prenatal vitamin with 400 IU of vitamin D. At 3 years of age, children of the women who received vitamin D supplements had lower levels of antibodies associated with allergy and asthma, as well as a small, but nonsignificant, decrease in rate of recurrent wheezing.[770] NHLBI is continuing to fund the study to follow these children up to the age of 6 years to examine the possible long-term effects of maternal vitamin D on their lung function.

The first enrollments of participants in the Vitamin D Supplementation in Children with Obesity-Related Asthma (VDORA1) trial have begun. Researchers at 16 IDeA Program States Pediatric Clinical Trials Network (ISPCTN) sites seek to better understand the pharmacokinetics of Vitamin D in children with both obesity and asthma to identify ideal Vitamin D dosing.[771] With this information, ISPCTN researchers will be able to design a trial to explore whether Vitamin D can be used to improve asthma symptoms in children with both obesity and asthma.

A study conducted by AsthmaNet found that the use of acetaminophen to manage pain or fever in young children with asthma is not associated with exacerbations.[772] Prior observational studies had suggested that acetaminophen use might exacerbate asthma, which led some doctors to recommend against its use

[767] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-010.html.
[768] https://www.nhlbi.nih.gov/news/2018/short-term-increases-inhaled-steroid-doses-do-not-prevent-asthma-flare-ups-children.
[769] Jackson DJ, et al. *N Engl J Med* 2018;378(10):891-901. PMID: 29504498.
[770] Litonjua AA, et al. *JAMA* 2016;315(4):362-70. PMID: 26813209.
[771] https://www.nih.gov/echo/clinical-sites-idea-states-pediatric-clinical-trials-network.
[772] Sheehan WJ, et al. *N Engl J Med* 2016;375(7):619-30. PMID: 27532828.

in these children. The trial provides assurance to doctors and parents that they may safely prescribe acetaminophen to children with asthma who have fever, pain, or other discomfort typically alleviated with aspirin.[773]

NICHD is starting the second phase of a study to develop and preliminarily validate a novel intervention to be delivered in the high school setting that integrates two evidence-based, school-based interventions for urban adolescents.[774] In Phase I of this study, researchers developed and integrated school-based interventions to improve asthma self-management and sleep hygiene in urban high school students via interviews. In Phase II, the scientists intend to (1) evaluate the feasibility and acceptability of the intervention procedures and (2) assess the effects of the intervention on improving sleep quality in urban high school students with persistent asthma over a 2-month follow-up period.

Rural children experience the highest prevalence rate of asthma; they also face substantial burdens to asthma care, including lower socioeconomic status, more uninsured residents, and fewer health care providers. An RCT of an asthma education program delivered either through a weekly asthma class or an asthma day camp improved children's and their parent's asthma self-management, leading to fewer ED and office visits and lower rates of hospitalizations, compared with a control group who were provided weekly general health information.[775] The asthma classes and day camp also led to significant reductions of asthma symptoms, leading to reduction in asthma severity; these results remained significant more than 12 months after the training.

Allergy

An allergy is a reaction by the body's immune system to something that the body does not think belongs there but that does not bother most other people. People who have allergies are often sensitive to more than one thing. Allergies can cause a variety of symptoms—such as a runny nose, sneezing, itching, rashes, swelling, or asthma—that can range from minor to a life-threating response. In the U.S., allergies are the sixth leading cause of chronic illness, with more than 19.9 million adults and 5.6 million children diagnosed with hay fever in 2017 alone.[776] NIH supports allergy research, from basic research in specific allergy and immunology to epidemiological and observational studies to identify risk factors and to clinical trials that are testing new strategies to prevent and treat different allergies.

[773] https://www.nhlbi.nih.gov/news/2016/study-shows-acetaminophen-can-be-tolerated-young-children-mild-persistent-asthma.
[774] https://projectreporter.nih.gov/project_info_description.cfm?aid=9427957.
[775] Horner SD, et al. *J Rural Health.* 2016;32(3):260-8. PMID: 26431213.
[776] https://www.cdc.gov/nchs/fastats/allergies.htm.

Understanding Prevalence, Risk Factors, and Underlying Biology

Allergens are widespread, but highly variable in U.S. homes, according to the nation's largest indoor allergen study to date. Researchers from NIEHS report that more than 90 percent of homes had three or more detectable allergens, and 73 percent of homes had at least one allergen at elevated levels.[777]

Figure 51. A scientist in the NIAID Laboratory of Allergic Diseases prepares DNA from a specimen. Credit: NIAID.

Another recent study determined what differentiates dust mite allergens from the non-allergen proteins dust mites produce.[778] According to the researchers, dust mite allergens are more chemically stable and produced in larger quantities than other dust mite proteins. This study is the first to provide specific information about the characteristics of dust mite proteins and may help researchers uncover factors that lead to the development of dust mite allergy and assist in the design of better allergy therapies.

The bacterial products lipopolysaccharide and flagellin are present in common house dust and potently promote T helper (Th)2 and Th17 responses to common indoor allergens. Current studies are aimed at further understanding the molecular mechanisms that underlie bacterial product- and protease-mediated allergic sensitization through the airway, with an aim toward developing novel therapies targeted to distinct forms of asthma.[779]

NIAID-funded investigators determined that red meat allergies could be linked to a bite from the Lone Star tick, which can induce an allergic response against a sugar molecule called alpha-gal found in most mammalian meat.[780,781] A recent study led by NIAID scientists found that some cases of previously unexplained anaphylaxis (a life-threatening allergic reaction) were due to alpha-gal allergy, and that a diet free of red meat prevented anaphylaxis recurrence.[782] In June 2018, NIAID held a scientific agenda-setting

[777] Salo PM, et al. *J Allergy Clin Immunol* 2018;141(5):1870-9.e14. PMID: 29198587.
[778] Ogburn RN, et al. *J Allergy Clin Immunol* 2017;139(3):1030-2.e1. PMID: 27771129.
[779] https://www.niehs.nih.gov/research/atniehs/labs/iidl/pi/immuno-gen/studies/index.cfm.
[780] Carter MC, et al. *Allergy* 2018;73(5):1131-4. PMID: 29161766.
[781] https://www.niaid.nih.gov/news-events/niaid-scientists-link-cases-unexplained-anaphylaxis-red-meat-allergy
[782] https://clinicaltrials.gov/ct2/show/NCT00719719.

workshop on the prevention and treatment of alpha-gal allergy that identified research priorities in this field.

A new study using 5,000 stored blood samples found no increase in the presence of food-specific immunoglobulin E (IgE), a blood marker associated with food allergy, in children's blood between the 1980s and the 2000s.[783] The study suggests that the increases in prevalence of food allergies over the past several decades may be due to either an increase in the recognition and diagnosis of food allergy or to a changing relationship between the presence of IgE and food allergy symptoms.

Researchers have identified mutations in a gene called *CARD11* that lead to atopic dermatitis, or eczema, an allergic skin disease.[784] Scientists from NIAID and other institutions discovered the mutations in four unrelated families with severe atopic dermatitis and studied the resulting cell-signaling defects that contribute to allergic disease.[785] Each of the four families had a distinct mutation that affected a different region of the CARD11 protein, but all the mutations had similar effects on T-cell signaling. With cell culture and other laboratory experiments, the researchers determined that the mutations led to defective activation of two cell-signaling pathways, one of which typically is activated in part by glutamine. Their findings also suggest that some of these defects could potentially be corrected by supplementation with the amino acid glutamine.

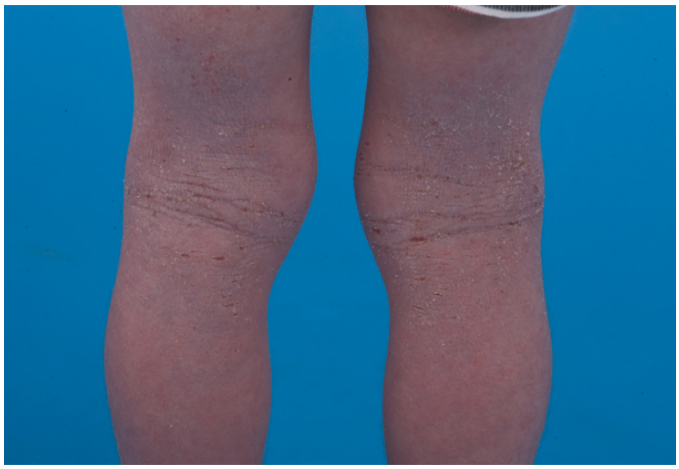

Figure 52. Eczema, also known as atopic dermatitis, is a chronic condition that causes the skin to become extremely itchy. Persistent scratching can lead to redness, blisters that weep clear fluid, bleeding, and crusting of certain areas of the skin. People with eczema also can be more susceptible to bacterial, viral, and fungal skin infections. Credit: NIAID.

Improving Treatment and Prevention

In a person with food allergy, the immune system reacts abnormally to a component of a food—sometimes producing a life-threatening response. Food allergies can be life-threatening, and avoiding

[783] McGowan EC, et al. *J Allergy Clin Immunol Pract* 2016;4(4):713-20. PMID: 27133095.
[784] Ma CA, et al. *Nat Genet* 2017;49(8):1192-1201. PMID: 28628108.
[785] https://www.niaid.nih.gov/news-events/scientists-identify-single-gene-mutations-lead-atopic-dermatitis.

allergens, particularly those frequently used in food preparation, can be challenging.[786] In 2017, an NIAID-sponsored expert panel issued clinical guidelines to aid health care providers in early introduction of peanut-containing foods to infants to prevent the development of peanut allergy.[787–789] This addendum to the 2010 Guidelines for the Diagnosis and Management of Food Allergy in the U.S. provides three separate guidelines for infants at various levels of risk for developing peanut allergy. Development of the Addendum Guidelines was prompted by emerging data from the landmark, NIAID-funded Learning Early About Peanut Allergy (LEAP) study,[790] suggesting that peanut allergy can be prevented by the early introduction of peanut-containing foods. Clinical trial results reported in February 2015 showed that regular peanut consumption begun in infancy and continued until 5 years of age led to an 81 percent reduction in development of peanut allergy in infants deemed at high risk because they already had severe eczema, egg allergy, or both.[791,792] In the follow-on LEAP-ON study,[793] all LEAP participants—both peanut consumers and peanut avoiders—were instructed to avoid peanut completely for 1 year. At age 6, following the avoidance period, children underwent an oral food challenge with peanut.[794] The clinical benefit seen in the peanut-consumer group persisted through this phase of the study, demonstrating that peanut tolerance achieved through early and regular peanut consumption is robust and durable.

Figure 53. Peanuts spilling off a plate. Credit: NIAID.

Similarly, a clinical trial supported partially by NIAID and NCATS investigated whether oral immunotherapy (OIT), wherein patients eat small, gradually increasing amounts of peanut protein daily, could suppress

[786] https://www.niaid.nih.gov/diseases-conditions/food-allergy.
[787] https://www.niaid.nih.gov/news-events/nih-sponsored-expert-panel-issues-clinical-guidelines-prevent-peanut-allergy.
[788] https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy.
[789] Togias A, et al. *J Allergy Clin Immunol* 2017;139(1):29-44. PMID: 28065278.
[790] http://www.leapstudy.co.uk.
[791] Du Toit G, et al. *N Engl J Med* 2015;372(9):803-13. PMID: 25705822.
[792] https://www.niaid.nih.gov/news-events/benefits-peanut-allergy-prevention-strategy-persist-after-one-year-peanut-avoidance.
[793] https://clinicaltrials.gov/ct2/show/NCT01366846.
[794] Du Toit G, et al. *N Engl J Med* 2016;374(15):1435-43. PMID: 26942922.

allergic immune responses to peanut. Nearly 80 percent of peanut-allergic preschool children successfully incorporated peanut-containing foods into their diets after receiving peanut OIT, with no allergic response.[795] Approximately 30 percent of people with food allergy are allergic to multiple foods. Another OIT study determined that adding an initial 16-week course of the medication omalizumab with OIT greatly improved the efficacy of OIT for children with allergies to multiple foods.[796] After 36 weeks of OIT, 83 percent of children who received omalizumab were able to eat at least 2 grams of two or more foods to which they were allergic relative to 33 percent of children who received a placebo. These results suggest that OIT is a safe and effective treatment for peanut-allergic preschoolers.[797,798]

Blood Diseases

NIH supports research on the causes, prevention, and treatment of nonmalignant blood diseases, including anemias, sickle cell disease (SCD), and thalassemia; premalignant processes, such as myelodysplasia and myeloproliferative disorders; hemophilia and other abnormalities of hemostasis and thrombosis; and immune dysfunction.

Chronic anemias result from a deficiency of red blood cells or an abnormality in hemoglobin production, as is the case with SCD and Cooley's anemia. Patients with chronic anemias can experience pain, fatigue, and other serious health problems. Chronic inherited bleeding disorders, such as hemophilia and von Willebrand disease, leave patients at risk for uncontrollable bleeding.

Hundreds of thousands of Americans suffer from one or more types of blood diseases. For example, in 2016 alone, more than 526,000 ED visits and 2.8 million physician office visits were made for anemia.[799] NIH's research into chronic blood disease leads to better understanding, treatment, and prevention of these disorders.

[795] Vickery BP, et al. *J Allergy Clin Immunol* 2017;139(1):173-81.e8. PMID: 27522159.
[796] Andorf S, et al. *Lancet Gastroenterol Hepatol* 2018;3(2):85-94. PMID: 29242014.
[797] https://www.niaid.nih.gov/news-events/oral-immunotherapy-safe-effective-treatment-peanut-allergic-preschoolers-study-suggests.
[798] https://www.niaid.nih.gov/news-events/omalizumab-improves-efficacy-oral-immunotherapy-multiple-food-allergies.
[799] https://www.cdc.gov/nchs/fastats/anemia.htm.

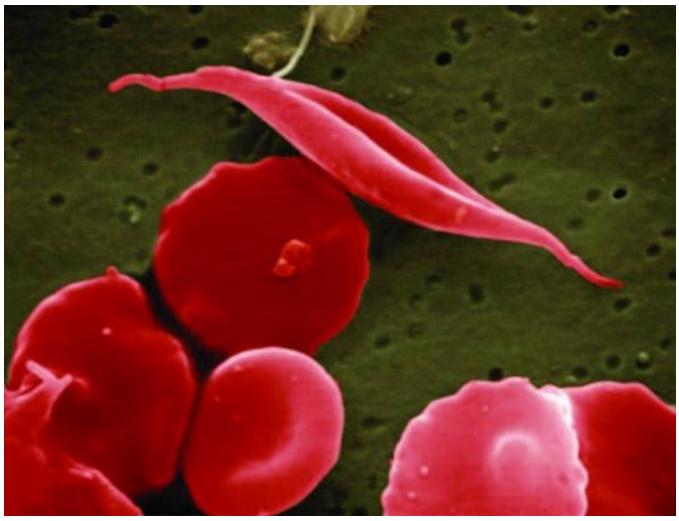

Figure 54. In sickle cell disease, a defect in hemoglobin (a protein that helps the cells carry oxygen through the body) causes red blood cells to become rigid and take on a crescent (sickle) shape, blocking small blood vessels and causing decreased blood flow, inflammation, pain, and strokes in children. Credit: NCATS.

Understanding Prevalence, Risk Factors, and Underlying Biology

The NIDDK-supported Stimulating Hematology Investigation New Endeavors (SHINE) program seeks to catalyze discoveries in basic molecular and cellular biology to provide new insights into the pathogenesis, prevention, detection, and potential treatment of benign hematologic diseases; to attract new investigators into basic and translational hematology research; to promote productive interdisciplinary research collaborations; and to reinforce interactions and communication between ICs and the hematology research community.[800] In FY 2016–2018, the following new research topics were added: Effects of Aging on Hematopoiesis, Metabolic Modulators of Hematopoiesis, Remodeling the Hematopoietic Stem Cell Niche, and Biology of Erythrocyte Maturation. SHINE findings include new models that predict the mature blood cell type of early stage blood cells,[801] as well as evidence that stem cell factor is selectively secreted by arterial endothelial cells in bone marrow—an example of endothelial cell heterogeneity in stem cell niches.[802]

In May 2018, NIDDK supported a workshop on *Beyond Transcriptomics: Understanding Erythrocyte Maturation.*[803] The purpose of this workshop was to explore approaches to bolster understanding of red blood cells beyond the recent progress that has been made using an approach called *transcriptomics*—the study of messengers, or transcripts, between genes and proteins that eventually carry out the instructions encoded in the genome. Workshop participants identified several research questions that, if

[800] https://grants.nih.gov/grants/guide/notice-files/NOT-DK-18-020.html.
[801] Tusi BK, et al. *Nature* 2018;555(7694):54-60. PMID: 29466336.
[802] Xu C, et al. *Nat Commun* 2018;9(1):2449. PMID: 29934585.
[803] https://www.niddk.nih.gov/news/meetings-workshops/2018/beyond-transcriptomics-understanding-erythrocyte-maturation.

answered, could move the field forward, including identification of factors that modify red blood cell structure and function in normal and diseased states.

Studies have linked increased sex hormone levels, such as during pregnancy or oral contraceptive use, with an increased risk of thrombosis—blood clotting that can cause a heart attack or stroke. In 2017, NHLBI launched a program to better understand the mechanisms of hormone-induced thrombosis.[804] Grants funded in 2018 are looking at how platelets (clotting cells) are activated during pregnancy and oral contraceptive use, new biomarkers for predicting thrombosis, and potentially protective mechanisms.

While characterizing samples obtained from 4,678 volunteers, NIDDK-supported researchers discovered 11 rare mutations in the *SH2B3* gene associated with higher hemoglobin and hematocrit levels.[805] To confirm that the *SH2B3* genetic mutation was responsible for the increased red blood cell production, two different genetic approaches were used to block the function of the gene in human embryonic stem cells and early stage red blood cells.[806] The results of the two genetic approaches confirmed that the *SH2B3* gene plays a mechanistic role in the ability of stem and early stage blood cells to develop into red blood cells in the laboratory. This newly acquired knowledge may contribute to future efforts to improve red blood cell production for medical applications such as replacement therapy during acute blood loss as a result of trauma or surgical procedures.

Sickle cell anemia is a chronic and debilitating disease that affects an estimated 100,000 people in the U.S., about a third of whom are children. People with SCD often suffer from acute and chronic pain, but little is known about the mechanisms of pain. Studying a mouse model of SCD, NHLBI-funded researchers found increased levels of an enzyme known as protein kinase C delta (PKCδ) in spinal cord neurons that normally regulate pain sensations.[807] Theorizing that PKCδ deactivates these neurons—and thus provokes pain—they gave the mice small-molecule inhibitors of the enzyme by spinal injections. Those treatments reduced measures of spontaneous pain, as well as responses to mild pressure or warming, suggesting that PKCδ is a key mediator of pain and could be an effective therapeutic target for pain relief.

During Sickle Cell Awareness Month each September, NHLBI plays a lead role in promoting activities that create awareness about the disease and research progress.[808,809] In 2017, this included NHLBI's first Facebook Live event, *Sickle Cell Research Directions: Advancing to a Widely Available Cure*, and the launch of the *Today's Faces of Sickle Cell Disease* campaign, which features real stories of strength and perseverance of people living with SCD, their loved ones, clinicians, and the researchers whose work offers

[804] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-003.html.
[805] Giani FC, et al. *Cell Stem Cell* 2016;18(1):73-8. PMID: 26607381.
[806] The NIH supports research using human embryonic stem cells within the NIH Guidelines for Human Stem Cell Research.
[807] He Y, et al. *J Clin Invest* 2016;126(8):3053-7. PMID: 27348590.
[808] https://www.nhlbi.nih.gov/directors-messages/national-sickle-cell-awareness-month.
[809] https://www.nhlbi.nih.gov/health-topics/education-and-awareness/sickle-cell.

hope for a cure.[810] NHLBI also develops related resources and engagement activities for a variety of audiences.

Figure 55. "Sickle Cell Disease": Infographic. Credit: NIH.

Improving Treatment and Prevention

In September 2018, NHLBI and its partners launched the Cure Sickle Cell (CureSC) Initiative,[811] a collaborative research effort to accelerate the development of genetic therapies to cure SCD. This followed on the heels of several engagement meetings with patients and other SCD stakeholders. The Initiative aims to bring genetic therapies into first-in-human clinical trials within 5 years.[812] The CureSC Initiative relies on a public–private partnership of patients, researchers, state and federal agencies, professional medical societies, biotechnology firms, and other private-sector partners all working together to accelerate curative therapies.[813]

NHLBI is participating in a multicenter nationwide study, which began in 2014, to test the effects of a novel gene-replacement therapy strategy to treat SCD.[814] The effort is similar to an approach that was undertaken by French researchers who reported in 2017 that they had reversed SCD in a 13-year-old boy. The experimental treatment involves removing hematopoietic (blood-forming) stem cells from the patient's bone marrow or blood and adding a therapeutic beta globin gene, which is defective in people with SCD.[815] The cells are then returned to the patient, leading to the production of potentially therapeutic

[810] https://www.nhlbi.nih.gov/news/2017/nhlbi-scientists-available-discuss-research-advances-during-national-sickle-cell.
[811] https://www.nhlbi.nih.gov/science/cure-sickle-cell-initiative.
[812] https://www.nhlbi.nih.gov/news/2018/nih-launches-initiative-accelerate-genetic-therapies-cure-sickle-cell-disease.
[813] https://www.nhlbi.nih.gov/news/2018/nhlbi-research-grants-advance-sickle-cell-treatment-lab-patients.
[814] https://clinicaltrials.gov/ct2/show/NCT02140554.
[815] Ribeil JA, et al. *N Engl J Med* 2017;376(9):848-55. PMID: 28249145.

levels of anti-sickling hemoglobin. Several patients at the NIH Clinical Center in Bethesda, MD, are participating in these studies.

The drug hydroxyurea has been approved by FDA to treat adults—but not children—with sickle cell anemia, although it is frequently prescribed off-label for children, especially older children, in capsule form. Measuring the concentration of hydroxyurea in the blood of 39 children with sickle cell anemia, researchers supported by NHLBI, NICHD, and the *Best Pharmaceuticals for Children Act* found that the liquid and capsule forms were equivalent and that dosages based on a child's weight provided consistent and predictable drug exposure.[816] The results of the study support approval of the drug in children and will help develop a liquid form for children who are unable to swallow a capsule.

Children with SCD live with an increased risk of stroke. The NHLBI Trans-Cranial Doppler (TCD) with Transfusions Changing to Hydroxyurea (TWiTCH) study found that in such children, the medication hydroxyurea is as effective as blood transfusions at reducing high TCD blood velocities, which are an indicator of stroke risk.[817] The results of the study showed that for high-risk children with SCD and abnormal TCD velocities, hydroxyurea can be taken instead of chronic blood transfusions to maintain TCD velocities and help prevent primary stroke.[818] This study provided the medical community with another option to treat children with SCD who are at the greatest risk of stroke.[819]

NHLBI-funded researchers are continuing to study genetic modifiers of SCD, particularly the regulation of the gene for fetal hemoglobin (HbF).[820] HbF is responsible for transporting oxygen during fetal life, but by about 6 months of age the body switches to making the adult form of hemoglobin (HbA), which is defective in people with SCD. Researchers have identified segments of DNA that are involved in regulating HbF production in adults. The work has implications for developing new ways to treat SCD, including new drug interventions and gene editing to stimulate HbF production.

Ongoing NIDDK-supported research seeks to identify approaches that reactivate HbF production to sufficient levels in adult red blood cells such that it compensates for the defects in hemoglobinopathies like SCD.[821] Using the CRISPR/Cas9 system, the protein called heme-regulated inhibitor (HRI) was shown to act as a repressor of HbF production. Specifically, HRI depletion in normal adult red blood cells resulted in significantly increased HbF levels. Furthermore, in subsequent experiments, the scientists found that HRI depletion in red blood cells from patients with SCD led to increases in HbF levels, which suggests that this strategy may be beneficial to people with SCD.

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[816] Estepp JH, et al. *J Clin Pharmacol* 2016;56(3):298-306. PMID: 26201504.
[817] https://www.nih.gov/news-events/news-releases/nih-ends-transcranial-doppler-tcd-transfusions-changing-hydroxyurea-twitch-clinical-trial-due-early-results.
[818] Ware RE, et al. *Lancet* 2016;387(10019):661-70. PMID: 26670617.
[819] https://www.nhlbi.nih.gov/news/2015/study-shows-hydroxyurea-viable-option-some-children-who-have-sickle-cell-anemia.
[820] Danjou F, et al. *Nat Genet* 2015;47(11):1264-71. PMID: 26366553.
[821] Grevet JD, et al. *Science* 2018;361(6399):285-90. PMID: 30026227.

A study reported using the CRISPR–Cas9 genome editing system to maintain HbF in human hematopoietic (blood-forming) stem cells.[822] The advance holds potential for reactivating HbF, which is normally switched off by about 6 months of age, as a means to compensate for deficiencies in HbA, the cause of SCD. The researchers' approach was inspired by a genetic condition called hereditary persistence of fetal hemoglobin (HPFH), which improves blood cell function when it occurs in people with SCD. The researchers isolated blood stem cells from people with SCD, used CRISPR-Cas9 to reproduce the mutation that causes HPFH, and thus reduced sickling of patient-derived blood cells.

In 2016, NHLBI launched the Hematopoietic Stem Cell Transplantation for Young Adults with Sickle Cell Disease (STRIDE-2), a multicenter study to compare survival and clinical outcomes in adolescents and young adults with severe SCD with those of patients who receive standard care from their SCD physician.[823] Hematopoietic stem cell transplantation—also known as a bone marrow transplant—is the only curative option for SCD, but it is still a difficult treatment for many patients, especially for those without a suitably matched donor. STRIDE-2 will compare the outcomes of the bone marrow transplant to standard care in hopes of broadening the therapeutic outcomes for adults with severe SCD.[824] NHLBI's intramural program is also working to improve bone marrow transplantation.[825] These studies have the potential to change the course of SCD in adult patients, who are less likely than children to benefit from established bone marrow transplant protocols.

Thanks to improved life expectancy among people with SCD, there is a need to better understand and optimize long-term treatment for adults with SCD. To help meet that need, NHLBI funded the development of a patient-reported outcome measurement system that assesses the physical, social, and emotional impact of SCD.[826] The Adult SCD Quality of Life Measurement Information System (ASCQ-Me) provides researchers and clinicians with high-quality data for use in intervention studies.[827]

To address barriers in the adoption of guideline-based care for people with SCD,[828] NHLBI launched the SCD Implementation Consortium (SCDIC) in 2016.[829] The SCDIC comprises eight clinical sites across the U.S. that are examining barriers to care and strategies to enhance health outcomes for adolescents and adults living with SCD.[830]

More than 75 percent of newborns who have SCD are born in sub-Saharan Africa. By funding the Sickle Cell Disease in Sub-Saharan Africa Collaborative Consortium and associated data coordinating center,

[822] Traxler EA, et al. *Nat Med* 2016;22(9):987-90. PMID: 27525524.
[823] https://clinicaltrials.gov/ct2/show/NCT02766465.
[824] Fitzhugh CD, et al. *Blood Adv* 2017;1(11):652-61. PMID: 29296707.
[825] https://www.nhlbi.nih.gov/health-topics/blood-and-bone-marrow-transplant.
[826] http://www.healthmeasures.net/explore-measurement-systems/ascq-me.
[827] Evensen CT, et al. *Medicine* 2016;95(35):e4528. PMID: 27583862.
[828] https://www.nhlbi.nih.gov/science/blood-disorders-and-blood-safety.
[829] https://www.nhlbi.nih.gov/news/2016/nhlbi-awards-grants-help-improve-health-outcomes-teens-adults-sickle-cell-disease.
[830] https://scdic.rti.org/.

NHLBI is helping to build the regional capabilities to research SCD and monitor patients in Africa.[831] These efforts may ultimately identify opportunities to improve treatment and care for all populations with SCD.

NHLBI's Recipient Epidemiology and Donor Evaluation Study (REDS)-III program conducts laboratory and epidemiological research to enhance the safety and availability of the blood supply, and the safety and effectiveness of transfusion therapies.[832] The program has developed the nation's largest database on blood transfusion, which is one of the most common medical procedures during hospitalization. The database combines recipient, blood component, and donor information from 4 major blood centers and 12 community and academic hospitals. It has already yielded results in a 2-year pilot that may lead to improvements in transfusion practices and patient health outcomes.[833] The REDS program also has an international component that includes activities in Brazil, China, and South Africa.

An international collaboration of two research teams, partly supported by the CTSA program at NCATS, built on a previous study that tested gene therapy for a patient with transfusion-dependent beta-thalassemia by conducting companion Phase II clinical trials with 22 patients who had severe beta-thalassemia. Beta-thalassemia is a common, genetic blood disorder that reduces the production of hemoglobin, which is the iron-containing protein in red blood cells that carries oxygen to cells throughout the body. The teams followed the patients' outcomes for 15 to 42 months and found that nine of the patients had the most severe form of beta-thalassemia, with two copies of genes that eliminate beta-globin production. After gene therapy, this group experienced a 74-percent reduction in annual blood transfusions; three of these patients were able to stop receiving transfusions entirely.[834] Thirteen of the patients had a slightly less severe form of the disease. None of these patients needed blood transfusions following the treatment.[835] Patients reported only the typical cell transplant-related side effects, suggesting that the treatment is safe. The team has made protocol modifications for a Phase III trial, which is now recruiting patients. Thirteen of the 22 patients from the current trials have also enrolled in a 13-year follow-up study to continue monitoring the safety and effectiveness of the treatment.

A team of researchers found a potential new drug treatment for people with bone marrow failure caused by rare telomere disorders.[836] Telomeres are the ends of our chromosomes and protect them from damage. Telomere shortening occurs with aging and has been linked to increased disease risk; it also occurs in some hereditary disorders that lead to bone marrow failure. In an NIH intramural study, scientists administered the synthetic sex hormone danazol to a small group of participants with bone marrow failure due to telomere disorders. In addition to slowing telomere loss, the drug unexpectedly appeared to elongate telomeres in almost all study participants. The treatment also improved blood

[831] https://www.nhlbi.nih.gov/science/blood-disorders-and-blood-safety.
[832] https://www.rti.org/impact/recipient-epidemiology-and-donor-evaluation-study-iii-reds-iii.
[833] Karafin MS, et al. *Transfusion* 2017;57(12):2903-13. PMID: 29067705.
[834] Thompson AA, et al. *N Engl J Med* 2018;378(16):1479-93. PMID: 29669226.
[835] https://www.nih.gov/news-events/nih-research-matters/gene-therapy-reduces-need-transfusions-severe-blood-disorder.
[836] Townsley DM, et al. *N Engl J Med* 2016;374(20):1922-31. PMID: 27192671.

counts in most study participants, and some who were dependent on blood transfusions no longer required them.[837]

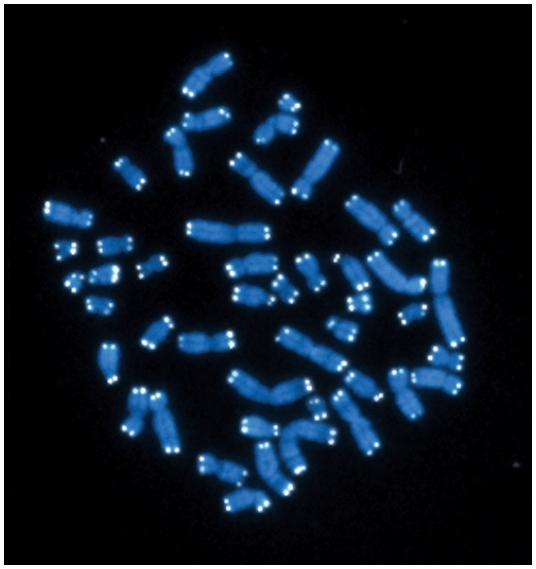

Figure 56. The 46 human chromosomes are shown in blue, with the telomeres appearing as white pinpoints. Credit: Hesed Padilla-Nash and Thomas Ried, NCI.

For the first time, a mutation in the gene encoding the small protein hormone erythropoietin (EPO) was discovered in a 6-year old boy with severe anemia. The parents of the 6-year old boy subsequently had a newborn who also had anemia, and testing confirmed that the newborn carried the same EPO mutation. NIDDK-supported clinical scientists developed a treatment strategy consisting of normal EPO, and after 11 weeks of treatment, the child's red blood cell production had increased—eliminating the need for blood transfusions.[838]

Chuvash polycythemia is an inherited life-threatening disorder characterized by overproduction of red blood cells and similar to mountain sickness, a blood complication experienced in high-altitude settings with low oxygen levels. Using a mouse model of Chuvash polycythemia, researchers found that feeding the mice a diet containing an experimental drug (Tempol) for 3 to 6 months decreased the animals' red blood cell levels, and disease symptoms (reddish, swollen paws and snouts) went away. Next, to mimic mountain sickness, normal mice were placed in low-oxygen housing for 23 days and developed polycythemia; all five of the mice that were fed a Tempol-supplemented diet survived, whereas two of five mice with a regular diet died. These findings offer hope that Tempol, or a similar drug, may treat similar disorders that affect human beings, such as mountain sickness.[839]

Current protein replacement therapies for hemophilia B, a genetic bleeding disorder caused by a deficiency in coagulation factor IX, rely on IV injections and infusions. Oral delivery of factor IX is a desirable needle-free option, especially for prophylaxis. NIBIB-funded researchers developed a pill to treat

[837] https://www.nhlbi.nih.gov/news/2016/study-shows-telomere-length-humans-can-be-altered-medical-drugs.
[838] https://www.ncbi.nlm.nih.gov/pubmed/?term=28283061.
[839] https://www.ncbi.nlm.nih.gov/pubmed/?term=29480820.

this serious inherited bleeding disorder.[840] Oral delivery of the treatment—clotting factor IX—would allow individuals with type B hemophilia to swallow a pill rather than be subjected to several weekly injections of factor IX to control potentially fatal bleeding episodes.[841] This work could possibly lead to an orally administered prophylactic treatment for hemophilia B patients.

Cardiovascular Diseases

Cardiovascular disease (CVD) is a broad term used to encompass many conditions, including heart diseases (e.g., coronary heart disease, cardiomyopathy, heart failure, heart valve disease, sudden cardiac arrest, congenital heart defects), cerebrovascular disease (including stroke), and other disorders and conditions of the blood vessels (e.g., peripheral arterial disease, deep vein thrombosis). Heart disease is the single largest cause of death among men and women in the U.S. Around one-quarter of deaths annually—about 630,000 per year—are caused by heart disease, and about half of Americans have at least one risk factor for heart diseases, such as diabetes, being overweight, poor diet, physical inactivity, or excessive alcohol use.[842]

Understanding Prevalence, Risk Factors, and Underlying Biology

Hypertension (high blood pressure) is one of the 10 most common chronic diseases in childhood, and it predisposes children to adult hypertension. Researchers supported by NICHD analyzed the electronic health records of 400,000 children from nearly 200 pediatric primary care sites across the country. Only 23 percent of children who had blood pressures consistent with hypertension at multiple primary care visits were diagnosed with the disease, and only 10 percent of patients with symptoms of prehypertension were diagnosed. Of children and adolescents with a diagnosis of hypertension for at least a year, only 6 percent of those who needed anti-hypertension medication received a prescription, suggesting that hypertension and prehypertension were infrequently diagnosed among pediatric patients.[843]Similarly, NIEHS supports the development of toxicology assays for cardiac differentiation iPSCs.[844] These efforts monitor the effects of toxicants on cardiomyocyte differentiation and cardiac formation. NIEHS grantees are continuing to develop an approach or assay for screening the effects of toxicants on early cardiac cell differentiation (cardiomyocytes, vascular endothelial cells, and vascular smooth muscle cells) derived from human iPSCs from multiple donors. The assay consists of fluorescent reporters for key proteins involved in cell differentiation and will be developed and tested using approximately 80 chemicals from the Tox21 compound library.[845]

[840] https://www.ncbi.nlm.nih.gov/pubmed/?term=27863665.
[841] https://www.nibib.nih.gov/news-events/newsroom/capsule-severe-bleeding-disorder-moves-closer-reality.
[842] https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_disease.htm.
[843] Kaelber DC, et al. *Pediatrics* 2016;138(6). pii: e20162195. PMID: 27940711.
[844] https://projectreporter.nih.gov/project_info_description.cfm?aid=9221318&icde=43187617.
[845] https://ntp.niehs.nih.gov/results/tox21/index.html.

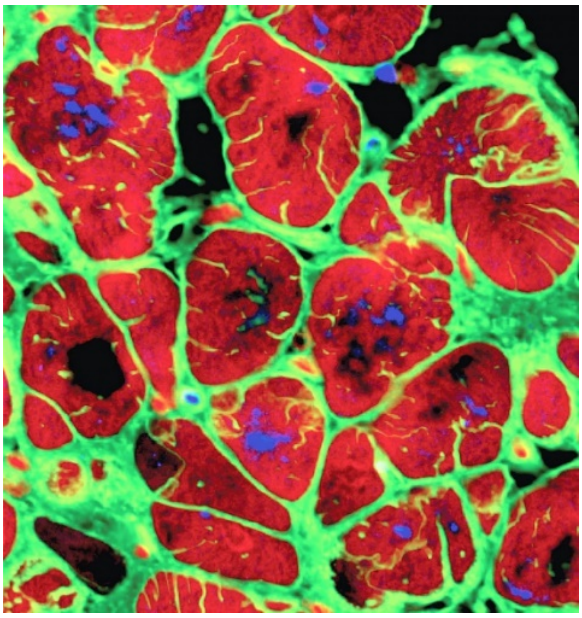

Figure 57. Adult-like cardiac tissue engineered from human pluripotent stem cells contains transverse tubules, the hallmark of maturity, seen in immunofluorescent images. Credit: Columbia University.

NIH's research efforts involve discovering the basic mechanisms of CVD, developing new tools for diagnosis, and seeking to understand risk factors for developing CVD. For example, echocardiography is crucial for establishing diagnoses, determining treatment options, monitoring disease progression, and assessing the effects of intervention in children with congenital and acquired heart diseases. The sizes of cardiovascular structures, however, often are affected by the abnormal hemodynamics of a disease state, particularly in children. Thus, clinicians need reliable, accurate, and generalizable normal reference values to make treatment decisions because they rely on an accurate determination of cardiovascular size. The Pediatric Heart Network (PHN), an NHLBI-supported group of hospitals in the U.S. and Canada, has produced normal reference values for standard pediatric echocardiographic measurements from a dataset on more than 3,000 infants, children, and adolescents from diverse racial and ethnic populations.[846] In growing children, clinicians assess the size of cardiac structures by using reference z-scores, which represent a range of cardiac sizes appropriate for the child's body size. The challenge is that z-score sets are available based on small studies, which can lead to very different assessments of whether the heart looks normal. The PHN's dataset is sufficiently large and diverse to eliminate this problem.[847]

Affecting approximately 800,000 people in the U.S. each year, a stroke is a medical emergency that occurs when a blood vessel supplying blood to part of the brain is blocked or damaged, depriving the brain tissue of oxygen and nutrients. Often, a stroke damages brain tissue in a specific region of the brain, resulting in a focal lesion. To determine how this focused damage may affect areas throughout the brain, researchers used MRI, which measures the locations of stroke lesions in the brain, and functional connectivity, which

[846] Lopez L, et al. *Circ Cardiovasc Imaging* 2017;10(11). pii: e006979. PMID: 29138232.
[847] http://www.pediatricheartnetwork.org/.

shows how different areas of the brain function together as part of the same network.[848] They created two models: The model using lesion locations could better predict motor and visual impairments, and the model using functional connectivity data could better predict deficits in verbal and visual memory. Both models predicted language and attention deficits well. This study links the effects of stroke on brain physiology to how brain networks are organized.

As the nation's largest study looking at CVD risk factors in African Americans, [849] the Jackson Heart Study is providing data to help better understand, prevent, and treat CVD in the Jackson, Mississippi, area and nationwide.[850,851] Since its launch in 1998, the study has collected extensive data on physiological, behavioral, socioeconomic, and sociocultural risk factors for CVD in African Americans and has used this information to improve cardiovascular health in this population. For example, in order to explore links between depression and cardiovascular disease in African Americans, researchers assessed symptoms of depression among 3,000 Jackson Heart Study participants and monitored their cardiovascular health for the next 10 years. The researchers found that major depressive symptoms were associated with greater risks of incident stroke and coronary heart disease after adjustment for clinical and behavioral risk factors.[852] Considering that African Americans with heart disease and stroke are likely to have poorer outcomes and later diagnoses than other groups, depression could be a useful warning sign for earlier detection of cardiovascular risk in this population. In August 2018, NHLBI renewed its support for the Jackson Heart Study.[853] The 2018–2024 phase of the study adds a new dimension by exploring the link between cardiovascular health and brain health, as well as the risk factors associated with cognitive decline. The Jackson Heart Study also seeks to build research capabilities in minority institutions, address the critical shortage of minority investigators in epidemiology and prevention, and reduce barriers to dissemination and use of health information in a minority population. New awards have an even stronger focus on community engagement to ensure that all Mississippians, not only the people of Jackson, are seeing benefits from the study and, in turn, that their participation is supporting science that will continue to benefit other communities across the U.S.

A leading cause of maternal mortality—severe postpartum hemorrhage—is on the rise in the U.S., yet routine reviews of mortality associated with childbirth have shown that many maternal deaths caused by hemorrhage are likely preventable. NICHD supports approximately 60 percent of NIH research on maternal health. Researchers analyzed data on more than 55 million deliveries, from 1998 to 2011, from a nationally representative sample of U.S. hospitals with low, moderate, or high volumes of deliveries. They found that a hospital's volume of deliveries was not a major risk factor for hemorrhage.[854] During the 14-year study period, the rate of postpartum hemorrhage was stable, but rates of transfusion and hemorrhage-related morbidity had risen. Meanwhile, in another NICHD-supported study using a large dataset of electronic medical records from an insurer in Northern California, researchers compared

[848] Siegel JS, et al. *Proc Natl Acad Sci USA* 2016;113(30):E4367-76. PMID: 27402738.
[849] https://www.nhlbi.nih.gov/science/jackson-heart-study-jhs.
[850] Divers J, et al. *BMC Genet* 2017;18(1):105. PMID: 29221444.
[851] Bell RA, et al. *J Racial Ethn Health Disparities* 2018;5(6):1230-7. PMID: 29427252.
[852] O'Brien EC, et al. *Circ Cardiovasc Qual Outcomes* 2015;8(6):552-9. PMID: 26578621.
[853] https://www.nhlbi.nih.gov/news/2018/nih-announces-awards-next-phase-jackson-heart-study.
[854] Merriam AA, et al. *J Matern Fetal Neonatal Med* 2018;31(8):1025-34. PMID: 28367647.

physicians' diagnoses of postpartum hemorrhage using the International Classification of Diseases (ICD) coding with data on the estimated amount of blood loss in women who had cesarean deliveries. The medical record data identified more women with significant blood loss (1.0 liters or more) than women who were formally diagnosed with postpartum hemorrhage using the ICD diagnosis codes.[855] This indicates that data from diagnostic codes can substantially underestimate the number of cases of postpartum hemorrhage. Under-diagnosis of postpartum hemorrhage was also more common when the patients were older women, Black women, women with obesity, and women with other types of serious pregnancy complications.

Another leading cause of maternal mortality and severe illness in the U.S. is obstetric venous thromboembolism (VTE), or blood clots in the veins, which can be fatal if they break loose and travel to the lungs or brain. To determine the risk of VTE after postpartum hospital discharge, researchers analyzed nationally representative data on hospital readmissions for VTE and found that the risk of readmission was highest in the first 10 days after discharge, with two-thirds of VTEs occurring by 20 days after discharge.[856] A patient's prior history of VTE was the most frequent risk factor for readmission, but only a small number of the readmissions (6 percent) were associated with prior VTE. Multiple other risk factors were associated with modestly increased probability of VTE readmission—including older maternal age, cesarean delivery, and hemorrhage with transfusion during delivery admission—with significant differences in risk based on socioeconomic status, geographic location, and insurance status.

Revised guidelines from the American Heart Association and American College of Cardiology now have four categories for blood pressure (BP) measurements: normal (BP below 120/80 mmHg), elevated, stage 1 hypertension, and stage 2 hypertension (most severe, with BP above 140/90 mmHg). Hypertension, or high blood pressure, during pregnancy significantly raises risks of potentially serious complications; however, the revised guidelines did not include much information on hypertension during pregnancy. Using a large clinical trial of low-dose aspirin in pregnant women expecting their first child, researchers analyzed data using the stage 1 definition of hypertension, finding that the risk of pregnancy complications, even at this relatively low level of elevated blood pressure, is higher than previously thought.[857] In addition, the women with elevated stage 1 hypertension had an increased likelihood of gestational diabetes mellitus and more medically necessary preterm deliveries, suggesting that even comparatively mild increases in blood pressure during pregnancy carry significant risk for both mother and child.

Treating hypertension in pregnant women with beta blockers (one type of antihypertensive drug) poses significant health risks for their newborn infants, according to a study of Medicaid claims data from approximately 2.2 million pregnancies in 46 states and the District of Columbia. Scientists found an estimated 70 percent increased risk of low blood sugar (hypoglycemia) in newborns of women taking the medications around the time of birth, compared to newborns of non-medicated mothers.[858] Moreover,

[855] Butwick AJ, et al. *Transfusion* 2018;58(4):998-1005 PMID: 29377131.
[856] Wen T, et al. *Am J Obstet Gynecol* 2018;219(4):401.e1-401.e14. PMID: 30017675.
[857] Sutton EF, et al. *Obstet Gynecol* 2018;132(4):843-9. PMID: 30204698.
[858] Bateman BT, et al. *Pediatrics* 2016;138(3). pii: e20160731. PMID: 27577580.

the research showed a 30 percent increased risk of abnormally low heart rate (bradycardia) in these newborns. Hypertensive disorders complicate 5 percent to 10 percent of all pregnancies and are associated with significant maternal and fetal disorders, but the risks and benefits of using beta blockers during pregnancy are controversial.

Preeclampsia, a dangerous pregnancy complication related to high blood pressure, affects about 5 percent of pregnancies, contributing to nearly 15 percent of maternal deaths and 25 percent of deaths of infants during or shortly after birth. Because preeclampsia shares similar pathological characteristics with CVD, researchers supported by NICHD and NCATS conducted a small, controlled clinical trial of pravastatin, a drug typically used to reduce the risk of CVD, in 20 pregnant women with a history of prior preeclampsia, who were at a high risk for recurrence. None of the women taking pravastatin developed preeclampsia, although four in the placebo group did develop the condition—about the same rate as in the general population—with no identifiable safety risks associated with the drug.[859] Researchers are continuing this research with higher dose to fully assess the safety and effectiveness of pravastatin for preventing preeclampsia in high-risk pregnant women.

Women who have a myocardial infarction (MI) at a younger age are more likely to have adverse cardiovascular outcomes than young men who have had an MI, but the reasons for this are unclear. An NHLBI-funded study found that following an MI, young women are twice as likely as men of a similar age to develop mental stress–induced myocardial ischemia—a shortage of blood flow to the heart during emotional distress—and vascular disease.[860] This information can be used for future efforts to improve screening. Similarly, heart failure with preserved ejection fraction (HFpEF) afflicts more women than men and is resistant to treatments that work for other types of heart failure. NHLBI held a workshop in September 2017 to address these sex differences and to explore new preventive, diagnostic, and therapeutic strategies for HFpEF.[861] One future strategy will be to encourage patient-specific phenotyping that may provide a better understanding of the differences in disease manifestation between women and men.

Women with endometriosis, an often-painful gynecologic condition, are more likely also to have two risk factors linked to heart disease: an unfavorable cholesterol profile and a high level of inflammation. An NICHD and NCI analysis of two decades of data from the very large Nurses' Health Study II found that women with endometriosis were at increased risk for heart disease.[862] Much of this risk could be accounted for by the increased frequency and earlier age at which women with endometriosis had it treated surgically, with removal of the uterus and ovaries. In effect, the women experienced surgical menopause, and early loss of ovaries and extended use of hormone therapies to treat menopausal symptoms are each independently associated with increased risk of heart disease. The research supported recommendations that women with endometriosis receive periodic checkups for early stages of heart disease and consider a heart-healthy lifestyle.

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[859] Costantine MM, et al. *Am J Obstet Gynecol* 2016;214(6):720.e1-720.e17. PMID: 26723196.
[860] Vaccarino V, et al. *Circulation* 2018;137(8):794-805. PMID: 29459465.
[861] https://www.nhlbi.nih.gov/events/2017/research-priorities-heart-failure-preserved-ejection-fraction-hfpef.
[862] Mu F, et al. *Circ Cardiovasc Qual Outcomes* 2016;9(3):257-64. PMID: 27025928.

Each year, more than 400,000 women in the U.S. undergo hysterectomy (removal of the uterus), mostly for noncancerous (benign) disorders. Whereas earlier practice typically included removal of the ovaries in the course of hysterectomy, current practice emphasizes retaining the ovaries, particularly in premenopausal women. Prior studies have shown that surgical removal of healthy ovaries tends to increase women's risk of CVD. Researchers supported by NICHD and NIA analyzed electronic health record data on more than 2,000 women who had undergone hysterectomy with ovarian conservation for benign indications, compared with women who had not had surgical removal of the uterus or ovaries.[863] The results showed that women who undergo hysterectomy are at elevated risk of cardiovascular and metabolic disorders in the years following their surgery, even when the ovaries are conserved.

An NINR-supported study of women without known coronary heart disease, the administration of the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAP-MISS), identified key symptoms that could help predict cardiac events in the short term (within 90 days).[864] The study identified arm pain or discomfort and unusual fatigue as symptoms associated with future cardiac events.

Decades of fundamental research on how the heart develops in early life are leading to exciting gains in understanding atrial fibrillation (AFib). AFib is the most common type of rapid, irregular heartbeat in the U.S. and a risk factor for stroke and heart failure. Many advances in AFib treatment have occurred, but earlier intervention is needed, especially for women, who have higher rates of death and disability from AFib than men do. Recently, in a large GWAS, that included about 60,000 people with AFib, NHLBI-funded researchers found that a number of genes known to be involved in heart development during early life also are associated with susceptibility to AFib.[865, 866] These genes could help identify people at risk for AFib and serve as targets for more effective therapies.

NHLBI-funded researchers found that heart failure (HF) patients were less likely to improve following treatment if they carried a particular variant of the hypocretin (orexin) receptor gene.[867] The investigators replicated this genetic variant in a mouse model of HF and found that cardiac function could be rescued using a drug that stimulates the orexin receptor. This is the first report of a sleep gene linked to disease outside of the brain. The findings may help explain why some heart failure patients improve with medical management while others worsen. A similar study, which analyzed data from 1,412 participants under age 65 across six U.S. communities in NHLBI's Multi-Ethnic Study of Atherosclerosis (MESA), revealed that increasing severity of untreated, abnormal breathing patterns during sleep is associated with greater left ventricular (LV) mass and LV mass/volume ratio in both men and women.[868] Prior studies had demonstrated associations in men but not women or had found stronger associations in men. These findings support the need to consider obstructive sleep apnea as a contributor to cardiac dysfunction in

[863] Laughlin-Tommaso SK, et al. *Menopause* 2018;25(5):483-92. PMID: 29286988.
[864] McSweeney JC, et al. *Womens Health Issues* 2017;27(6):660-5. PMID: 28830656.
[865] Ko D, et al. *Nat Rev Cardiol* 2016;13(6):321-32. PMID: 27053455.
[866] Nielsen JB, et al. *Nat Genet* 2018;50(9):1234-9. PMID: 30061737.
[867] Perez MV, et al. *J Am Coll Cardiol* 2015 Dec 8;66(22):2522-33. PMID: 26653627.
[868] Javaheri S, et al. *Sleep* 2016;39(3):523-9. PMID: 26888453.

women, and they suggest that future sleep apnea intervention studies aimed at reducing CVD risk should assess cardiac structure for both sexes.

In most cases, however, an individual's risk for developing common diseases, such as type 2 diabetes or heart disease, is polygenic, meaning that the risk depends on many genes in a person's genome. Researchers supported by NHGRI are actively developing and exploring the use of polygenic risk scores to identify which patients are at risk for such diseases. In one paper, researchers developed polygenic risk scores for several diseases, including coronary artery disease. They looked at more than 6.6 million spelling differences in the genome and combined them to make a polygenic risk score that could identify individuals with a fourfold increased risk for coronary artery disease.[869] Studies like these may contribute to future precision medicine strategies.

Transgender individuals are those whose gender identity differs from the male or female designation of sex they were assigned at birth. Cross-sex hormone therapies can support an individual's gender identity as a trans woman (male-to-female) or trans man (female-to-male). However, when researchers analyzed electronic health records from three large Kaiser health plans, they found that trans women enrollees had elevated rates of blood clots and, to a lesser extent, ischemic stroke, compared with cisgender female and male enrollees (those whose gender identity and sex at birth were consistent).[870] These rates were most pronounced among those who had begun estrogen therapy. MI rates in the trans women were also higher than those of cisgender women, but comparable to those in cisgender men.

Duchenne muscular dystrophy (DMD) is a genetic heart disease resulting from a mutation in the dystrophin gene. NIA-supported researchers found that mice lacking dystrophin have mild symptoms; however, when telomeres (protective structures at the ends of each chromosome) are reduced from the long lengths typical in mice to the short lengths typical in humans, the mice that lack dystrophin develop severe heart symptoms.[871] These findings suggest that shortened telomeres can contribute to disease of the heart muscle.

Pharmacogenomics refers to the use of genomic information to understand patients' response to drugs. Variants in the gene encoding cytochrome P450 (CYP) 2C19 enzyme, a key determinant in clopidogrel metabolism, can cause people to have different responses to clopidogrel, a very common anti-clotting drug that is prescribed to patients with heart disease and can prevent heart attacks. Patients with a broken *CYP2C19* gene achieve better outcomes on alternative anti-clotting drugs. Researchers analyzed the *CYP2C19* variants of approximately 1,800 patients who received stents and found that those who carried a broken *CYP2C19* variant and were switched to alternative treatment were half as likely to experience a major adverse cardiovascular event.[872]

Lupus survival rates have increased over the years, but women with lupus have a 50-fold increased risk of heart attack and CVD, compared to healthy women. A study conducted by NIAMS intramural researchers

[869] Khera AV, et al. *Nat Genet* 2018;50(9):1219-24. PMID: 30104762.
[870] Getahun D, et al. *Ann Intern Med* 2018;169(4):205-13. PMID: 29987313.
[871] Chang AC, et al. *Proc Natl Acad Sci USA* 2016;113(46):13120-5. PMID: 27799523.
[872] Moon JY, et al. *Expert Rev Clin Pharmacol* 2018;11(2):151-64. PMID: 28689434.

links low-density granulocytes, a distinct subset of neutrophils, to vascular damage and cardiovascular risk in lupus patients.[873] Data from the study support previous reports that neutrophils disrupt high-density lipoprotein function to promote plaque formation in blood vessels.

In a 2016 study, preclinical research funded by NIDA suggests that secondhand marijuana smoke may cause longer-lasting cardiovascular harm than secondhand tobacco smoke.[874] In this study, rats were exposed to secondhand marijuana or tobacco smoke at moderate to high levels (equivalent to secondhand tobacco exposure in restaurants that allow smoking). Blood vessel function was tested before and after exposure by measuring flow-mediated dilation (FMD), which is the extent to which arteries enlarge in response to increased blood flow. Dysfunctional FMD indicates potential cardiovascular impairment because proper FMD ensures sufficient blood flow through the heart and rest of the body. The researchers found that just one minute of exposure to secondhand marijuana smoke produced FMD impairment that lasted for at least 90 minutes.[875] In contrast, impairment from one minute of secondhand tobacco exposure was recovered within 30 minutes.

In 2018, NIEHS and NHLBI held a workshop[876] to bring together experts to discuss the state of the science pertaining to underlying biological pathways of the combined effects of chemical and nonchemical stressors associated with atherosclerosis, a disease known to be initiated by both types of stressors. NIEHS researchers are also exploring the relationship of physical and social environmental determinants of racial, ethnic, and socioeconomic disparities in cardiometabolic dysfunction and sleep health.[877]

Research supported by the Fogarty International Center looked at Framingham Risk Scores to compare postmenopausal women located in four countries. Researchers found that childbirth during adolescence may serve as a CVD risk marker; women who became mothers during adolescence may benefit from earlier and increased cardiovascular screening to reduce the incidence of cardiovascular events.[878]

Food and supplement intake may be associated with increased risk of CVD events. A 2017 NHLBI-funded study looked at more than 700,000 deaths from heart disease, stroke, and type 2 diabetes that occurred among U.S. adults in 2012. An estimated 45.4 percent of these deaths were associated with suboptimal intake of 10 food and nutrient groups.[879] The highest number of deaths were related to a high intake of sodium (9.5 percent), followed by low nuts/seeds, high processed meats, low seafood omega-3 fatty acids, low vegetables, low fruits, and high sugary drinks.

Researchers analyzed data from more than 2,700 people 45 to 84 years of age from NHLBI's long-running MESA and found that a diet high in calcium-rich foods was associated with lower risk of atherosclerosis.

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[873] Carlucci PM, et al. *JCI Insight* 2018;3(8). pii: 99276. PMID: 29669944.
[874] https://www.drugabuse.gov/news-events/news-releases/2016/07/secondhand-marijuana-smoke-may-impair-cardiovascular-function.
[875] Wang X, et al. *J Am Heart Asso* 2016;5(8). pii: e003858. PMID: 27464788.
[876] https://www.niehs.nih.gov/news/events/pastmtg/2018/stressors/index.cfm.
[877] https://projectreporter.nih.gov/project_info_description.cfm?aid=9781327&icde=46731210&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=.
[878] Rosendaal NTA, et al. *J Am Heart Assoc* 2017;6(11). PMID: 29092844.
[879] Micha R, et al. *JAMA* 2017;317(9):912-24. PMID: 28267855.

However, the researchers also found that taking calcium in the form of supplements may raise the risk of plaque buildup in arteries and heart damage.[880] The study included White, African American, Hispanic, and Chinese American participants who completed dietary questionnaires and two CT scans, 10 years apart, to measure calcium deposits in the coronary arteries.[881] The study findings emphasize why patients should consult with a knowledgeable physician before taking calcium supplements.

Improving Treatment and Prevention

A majority of deaths from CVD are associated with rupture of plaque lining an artery. Thin-cap fibroatheromas (TCFAs) are a type of plaque that is prone to rupture but that cannot be detected in real-time in clinical settings. To detect TCFAs, NHLBI-funded researchers developed a minimally invasive imaging method that uses a combination of ultrasound and optical coherence tomography.[882] This ultrafast imaging of arteries with high resolution and deep penetration depth provides new opportunities to evaluate in real-time the risk posed by plaques, detect vulnerable plaques, and optimize treatment decisions.

About 6,000 children suffer in-hospital cardiac arrest each year in the U.S. Some clinicians have routinely used body cooling for patients in cardiac arrest because they believed it might lead to better outcomes. In this prospective randomized trial, researchers supported by NHLBI and NICHD studied 329 children, aged 2 days to 18 years, who suffered in-hospital cardiac arrest. They found no evidence of improved survival or better functional outcome with cooling, compared to maintenance of normal body temperature.[883]

Although most therapies for heart attack aim to reduce muscle loss, a newer strategy aims to replace muscle with heart tissue grown outside the body from human pluripotent stem cells. These tissue patches, however, have been too small to be useful. NHLBI-supported researchers recently developed a beating cardiopatch with contraction strengths approaching values recorded in adult heart muscle.[884] In rodent models, the cardiopatch was large enough to cover the heart, and the cells incorporated well and maintained their electrical and mechanical properties. Similarly, another NHLBI-funded group has pushed the boundaries of 3-D printing to develop a heart-on-a-chip. The chip contains a tissue-guiding layer that promotes assembly of cardiomyocytes (derived from rats or human pluripotent stem cells), plus built-in sensors to measure contraction.[885] The group was able to quantify contractile force and beating of this heart tissue in response to cardiac drugs, suggesting the device could be used to screen for potential new drugs.

Transcatheter aortic valve replacement (TAVR) is a minimally invasive procedure in which a doctor inserts a catheter in the leg or chest of a patient and guides it to the heart in order to replace a narrowed aortic

[880] https://www.hopkinsmedicine.org/news/media/releases/calcium_supplements_may_damage_the_heart.
[881] Anderson JJ, et al. *J Am Heart Assoc* 2016;5(10). pii: e003815. PMID: 27729333.
[882] Li J, et al. *Sci Rep* 2015;5:18406. PMID: 26678300.
[883] Moler FW, et al. *N Engl J Med* 2017;376(4):318-29. PMID: 28118559.
[884] Shadrin IY, et al. *Nat Commun* 2017;8(1):1825. PMID: 29184059.
[885] Lind JU, et al. *Nat Mater* 2017;16(3):303-8. PMID: 27775708.

valve that fails to open properly (aortic valve stenosis). TAVR has reduced the risk of complications of aortic valve replacement, compared with traditional open-heart surgery; however, these patients have a risk of blood clots and other complications of the valve. NCATS CTSA program support enabled the early development and de-risking of an innovative device that may be more durable and help patients avoid complications of the TAVR method for heart valve replacement.[886]

NINR supported researchers analyzed data from more than 200 individuals with heart failure to better understand the relationship between heart failure symptoms, medication adherence, and cardiac event–free survival. The researchers assessed the frequency of heart failure symptoms, such as difficulty breathing (dyspnea) and ankle swelling in the past 3 months, and cardiac events (involving hospitalization and cardiac death). The study found that many heart failure patients were noncompliant with their medications, which was significantly associated with increased heart failure symptoms.[887] Medication adherence was found to mediate the relationship between heart failure symptoms and cardiac event–free survival in heart failure. These findings highlight the importance of medication adherence in heart failure.

The NHLBI Cardiothoracic Surgical Trials Network (CSTN) facilitates cooperation of surgeons around the country through infrastructure that supports proof-of-concept studies and interventional protocols for patients with cardiovascular disease.[888] In 2017, the American College of Cardiology and American Heart Association used the CSTN to update their guidelines for the management of valvular heart disease. The recommendations were modified to recommend that patients with ongoing, severe valve leakage have the valve replaced rather than repaired during a coronary artery bypass. NHLBI is renewing the network as a flexible platform that will extend its scope and impact by expanding training of early-stage investigators and reach into areas of high disease burden. During the 7-year renewal, a broad reach of investigators and industry collaborators will have an opportunity to access the network. The CSTN also will conduct implementation research alongside its clinical trials; these studies will examine strategies for optimal uptake and sustainability of cardiac procedures and devices in diverse vulnerable populations.

Congenital heart disease is the most common birth defect in the U.S. With advances in medicine, many children with congenital heart disease are living well into adulthood, and NHLBI continues to support research on the causes of congenital heart disease and its effects across the lifespan. NHLBI's Bench to Bassinet Program leads these efforts, with the PHN serving as the clinical cornerstone. Network researchers recently completed a study to improve post-surgical management for two common heart defects: tetralogy of Fallot and coarctation (narrowing) of the aorta. Through a collaborative learning approach, five centers in the network examined and updated their practices for breathing tube removal after surgery.[889] The new practices cut the typical amount of time infants spent with a breathing tube by nearly 80 percent and helped reduce medical costs by an estimated 27 percent—or $13,500 per surgery.

[886] https://ncats.nih.gov/pubs/features/ctsa-foldavalve.
[887] Wu JR, et al. *J Cardiovasc Nurs* 2018;33(1):40-6. PMID: 28591004.
[888] http://www.ctsurgerynet.org.
[889] Mahle WT, et al. *Pediatr Crit Care Med* 2016;17(10):939-47. PMID: 27513600.

Black men have low rates of hypertension treatment and the highest rate of hypertension-related death in the U.S. Previously, researchers found a slight reduction in blood pressure in men whose barbers had measured their blood pressure and encouraged those with high blood pressure to visit their doctor. In a new study, NHLBI-funded researchers built on that progress by adding pharmacist consultations to the barber shop intervention. Compared to a control group of participants who received encouragement from their barber to adopt healthy lifestyle changes and make doctor appointments, participants with access to a pharmacist through their barber shop had a 21.6 mmHg greater mean reduction in blood pressure.[890,891]

The NHLBI Systolic Blood Pressure Intervention Trial (SPRINT)[892] found that intensive blood pressure treatment can reduce heart attacks, strokes, and death in high-risk adults over age 50.[893, 894] In 2016, NHLBI opened access to the SPRINT dataset used in the primary results paper and hosted the SPRINT Data Analysis Challenge in partnership with the *New England Journal of Medicine*.[895] Researchers were challenged to test a new hypothesis or develop a new approach to patient care using the data. The Challenge attracted global participation, with approximately 16,000 followers on social media, 200 competing teams, and 3 final winners who presented at a national conference. The winning team developed a tool that enables clinicians to quickly assess whether intensive blood pressure management is appropriate for a specific patient. Also, a 2016 analysis of SPRINT data found benefits of aggressive blood pressure management for patients age 75 and older. Data from this trial led to a key update to the new 2017 Hypertension Clinical Practice Guidelines from the American Heart Association and the American College of Cardiology, which recommend that high blood pressure be treated earlier with lifestyle changes and, in some patients, medication.[896]

Scientists supported by NINR recruited inactive, urban, midlife African American women to a physical activity intervention that consisted of group meetings and possible follow-up motivational telephone calls. The women in the study had a higher number of CVD risks than the national average, including obesity, hypertension, and hypercholesterolemia. Women who participated in the intervention showed a significant increase in their physical activity 24 weeks after first receiving the intervention and maintained this increase at 48 weeks, regardless of whether they received follow-up telephone calls.[897] The study demonstrated a successful model for a face-to-face intervention with strong adherence to promote physical activity in an at-risk minority population.

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[890] https://www.nhlbi.nih.gov/news/2018/one-year-later-barbershop-intervention-continues-lower-blood-pressure-black-men.
[891] Victor RG, et al. *N Engl J Med* 2018;378(14):1291-1301. PMID: 29527973.
[892] https://www.nhlbi.nih.gov/science/systolic-blood-pressure-intervention-trial-sprint-study.
[893] SPRINT Research Group, et al. *N Engl J Med* 2015;373(22):2103-16. PMID: 26551272.
[894] https://challenge.nejm.org/pages/about.
[895] https://www.nejmgroup.org/wp-content/uploads/mar2017-data-summit.pdf.
[896] Williamson JD, et al. *JAMA* 2016;315(24):2673-82. PMID: 27195814.
[897] Wilbur J, et al. *Am J Health Promot* 2016;30(5):335-45. PMID: 27404642.

Figure 58. A SPRINT Participant has his blood pressure measured. Credit: Wake Forest School of Medicine.

In a study of symptoms experienced after stroke, researchers found differing patterns of poststroke depression among African American stroke survivors who had received inpatient rehabilitation. Fifteen percent of stroke survivors had poststroke depression; this number is lower than the rate of depression seen in the general population—around 30 percent.[898] Those with depression were also more likely to experience dysphagia and have recorded cognitive deficits. No significant association was found between depression and functional status at discharge. Understanding patterns of symptom experiences is important to the development of early interventions and treatment of poststroke depression.

Cardiac amyloidosis caused by deposition of amyloid fibrils from transthyretin is an increasingly recognized cause of HFpEF in older adults, particularly Black and Hispanic men. Novel noninvasive imaging now facilitates the early diagnosis and treatment of cardiac amyloidosis before irreversible damage is incurred by the amyloid depositions, both in the heart and around nerve canal space (carpal tunnel and lumbar stenosis).[899] Recently, two silencing RNA (siRNA) transthyretin silencers (patisiran and inotersen) were shown in a Phase III randomized trial to significantly decrease neurologic symptoms and improve quality of life.[900–902] These NIA-supported findings give hope for another class of therapy to reduce HFpEF and the poor quality of life, morbidity, and mortality associated with amyloid fibrils from transthyretin when diagnosed early.[903,904]

The NHLBI-funded Objective Physical Activity and Cardiovascular Health (OPACH) study found that both light-intensity and moderate–vigorous physical activity, as measured by an accelerometer, were associated with lower mortality in Women's Health Initiative participants aged 63–99 years.[905] The study

[898] Harris GM, et al. *J Stroke Cerebrovasc Dis* 2017;26(1):116-24. PMID: 27720524.
[899] Gillmore JD, et al. *Circulation* 2016;133(24):2404-12. PMID: 27143678.
[900] Maurer MS, et al. *Circ Heart Fail* 2017;10(6). pii: e003815. PMID: 28611125.
[901] Rosenblum H, et al. *Circ Heart Fail* 2018;11(4):e004769. PMID: 29615436.
[902] Maurer MS, et al. *Circ Heart Fail* 2015;8(3):519-26. PMID: 25872787.
[903] Castaño A, et al. *Congest Heart Fail* 2012;18(6):315-9. PMID: 22747647.
[904] Castaño A, et al. *JAMA Cardiol* 2016;1(8):880-89. PMID: 27557400.
[905] LaMonte MJ, et al. *J Am Geriatr Soc* 2018;66(5):886-94. PMID: 29143320.

helped inform a 2018 update to the Physical Activity Guidelines for Americans, enhancing the Guidelines' applicability for older women.

Research supported by the Fogarty International Center found that by using a newly created simulation model of diabetes and cardiovascular disease in Mexico—dubbed the *CVD Policy Model-Mexico*—investigators from the University of California, San Francisco, and the Instituto Nacional Salud de Publica in Cuernavaca, Mexico, estimated that the Mexican sugary beverage tax would prevent approximately 190,000 cases of diabetes, 20,000 heart attacks and strokes, and 19,000 deaths among Mexican adults aged 35–94 years over the next 10 years.[906, 907]

Chronic Fatigue

Chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis (ME), is a complex, multisymptom condition characterized by overwhelming fatigue that does not improve with bed rest and that may be worsened by physical or mental activity. CFS is diagnosed 2–6 times more often in women than in men. The condition is difficult to diagnose because of multiple diagnostic criteria used by various practitioners and the lengthy time frame for occurrence and recurrence of symptoms. CDC indicates that for a patient to be diagnosed with CFS, symptoms must have persisted or recurred during 6 or more consecutive months of illness.[908] NIH seeks to discover the basic mechanisms behind CFS, identify new treatments, and support research that will improve the lives of people who suffer from CFS.

In 2017, NIH awarded four grants to establish a coordinated scientific research effort on myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[909] The grants support the creation of a consortium comprising three collaborative research centers (CRCs) and a data management coordinating center. Each CRC will conduct independent research and collaborate on several projects, forming a network to help advance knowledge on ME/CFS.

Chronic Pain and Palliative Care

Although acute pain is a normal sensation triggered in the nervous system to alert a person to possible injury and the need to take care of one's self, chronic pain is different in that it persists for weeks, months, or even years. Chronic pain is now viewed as a chronic disease condition in the same manner as other chronic diseases covered in this section, and it is resistant to many medical treatments. It can—and often does—cause severe problems, affecting an individual's quality of life. The term palliative care describes

[906] Sánchez-Romero LM, et al. *PLoS Med* 2016;13(11):e1002158. PMID: 27802278.
[907] https://www.ucsf.edu/news/2016/11/404746/mexicos-soda-tax-could-reduce-diabetes-heart-disease-and-health-costs-new-study.
[908] https://www.cdc.gov/cfs/general/index.html.
[909] https://www.nih.gov/news-events/news-releases/nih-announces-centers-myalgic-encephalomyelitis-chronic-fatigue-syndrome-research.

medical care for those suffering serious illnesses, focusing on providing relief from the symptoms, such as pain, nausea, constipation, and trouble sleeping.

Figure 59. "Pain in the U.S.": Infographic. Credit: NCCIH.

Understanding Prevalence, Risk Factors, and Underlying Biology

As the population continues to age, the prevalence of chronic age-related diseases and conditions is expected to rise. A recent pair of FOAs jointly issued by NCI, NIA, and NINR is soliciting research to develop new tools, methods, and models focused on palliative care in geriatric populations and in a variety of care settings.[910,911] These FOAs are broad, covering everything from development of new palliative interventions to analysis of large datasets to identify barriers to implementation of palliative care.

The ability to feel pain comes from underlying mechanisms within the nervous system. However, when pain persists, it can become a debilitating health condition. Scientists do not fully understand how this type of chronic pain develops. Long-term pain and inflammation after nerve injury are triggered by a specific protein—dual leucine zipper kinase (DLK).[912] According to intramural researchers at NICHD and NCCIH, identifying the role of DLK could lead to insights on new ways to treat long-term pain without opioids.[913] The research team developed mice that lack DLK and compared how these animals and normal

[910] https://grants.nih.gov/grants/guide/pa-files/pa-18-503.html.
[911] https://grants.nih.gov/grants/guide/pa-files/pa-18-502.html.
[912] Wlaschin JJ, et al. *Elife* 2018;7:e33910. PMID: 29968565.
[913] https://www.nichd.nih.gov/newsroom/news/070318-DLK.

mice recovered from nerve injury. They found that mice missing DLK did not develop long-term pain after injury, nor did their spinal cords develop a hallmark of nerve inflammation called microgliosis.

A recent study examined measures of pain-related cognitive content (what people think about pain) and pain-related cognitive processes (how people think about pain; what they do with those thoughts) to determine the extent to which these measures are relatively independent and contribute unique variance to the prediction of patient function.[914] Using data from 165 participants with chronic low-back pain, analyses demonstrated that pain-related cognitive content and cognitive processes could be assessed as distinct components; however, measures assessing cognitive content (i.e., pain catastrophizing) demonstrated stronger associations with patient function than did measures of cognitive process (i.e., mindfulness). These results provide insight on potential mechanistic targets for behavioral approaches to pain management.

The NIH Common Fund has launched the Acute to Chronic Pain Signatures (A2CPS) program to investigate the biological characteristics underlying the transition from acute to chronic pain.[915] The effort will also seek to determine the mechanisms that make some people susceptible and others resilient to the development of chronic pain. The A2CPS program will collect data from patients with acute pain associated with a surgical procedure and from patients with acute pain from a musculoskeletal trauma, such as a broken bone.[916] Neuroimaging, high-throughput biomedical measurements, sensory testing, and psychosocial assessments collected periodically after the acute pain event will form a comprehensive dataset to help predict which patients will develop chronic pain. Using biological signatures to predict who might be at risk for developing chronic pain would be valuable in guiding precision medicine approaches to prevent chronic pain and, by doing so, would reduce reliance on opioids. A2CPS enhances the goals of the NIH HEAL Initiative, although the funds for A2CPS will be supplied by the Common Fund and therefore represent additional investment to enhance research on pain and opioid addiction beyond funds already allocated to HEAL. The first awards are expected in FY 2019.

Surrogate decision makers for the critically ill often experience intense emotional distress, impaired information processing, and other emotional symptoms. A group of researchers developed the first measurement tool for assessing decisional fatigue, the Decision Fatigue Scale, in surrogate decision makers for the critically ill.[917] A study of this new tool with a sample of surrogates found that the Decision Fatigue Scale was reliable with high validity. Tools like the Decision Fatigue Scale will be useful in measuring different levels of decisional fatigue in surrogate decision makers, which can help identify better strategies for clinicians to use when interacting with these individuals.

According to an analysis of data from the 2012 National Health Interview Survey (NHIS), American adults with some form of musculoskeletal pain are more likely to use complementary health approaches than people without one of these pain disorders.[918] More than half of American adults (125 million) had a

[914] Jensen MP, et al. *Clin J Pain* 2018;34(5):391-401. PMID: 28926413.
[915] https://commonfund.nih.gov/pain.
[916] https://www.nih.gov/news-events/news-releases/nih-research-program-explore-transition-acute-chronic-pain.
[917] Hickman RL Jr, et al. *West J Nurs Res* 2018;40(2):191-208. PMID: 28805132.
[918] Clarke TC, et al. *Natl Health Stat Report* 2016;(98):1-12. PMID: 27736632.

musculoskeletal pain disorder in 2012. However, the research also pointed out that some people with musculoskeletal pain disorders who use complementary health approaches do not necessarily use these approaches to treat their pain.

Recent research, funded in part by NCCIH, describes how acupuncture may achieve local pain-relieving effects in people with carpal tunnel syndrome (CTS) and showed the effects of the technique on the brain's pain centers.[919] The researchers found that both true and sham acupuncture reduced CTS symptoms, but true acupuncture was superior in improving peripheral and brain neurophysiologic outcomes.[920]

An NIDDK-led network called the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network comprises multiple centers that conduct innovative, collaborative studies of interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), including searching beyond the bladder/prostate to find the causes of these conditions and studying the possible relationships between these conditions and other chronic pain disorders (such as irritable bowel syndrome and fibromyalgia).[921] Several key discoveries have emerged from data collected during the network's first phase. The network characterized symptom variability in participants over time, which is critically important to the design of clinical studies and trials. It also amassed detailed body mapping of pelvic and nonpelvic pain in participants at baseline and—in combination with survey data about urologic, non-urologic, and psychosocial symptoms and quality of life—identified and characterized different pain pattern groupings and differences between women and men in these groups.[922,923] The network also developed a brain imaging analysis approach that correctly predicted symptom trends—both improvement and worsening—in 73 percent of study participants 3 months post-scan.[924] NIDDK, with co-sponsorship from the ORWH, renewed the network for a second 5-year phase in FY 2014 to continue studies that could provide a foundation for effective clinical interventions for people with IC/BPS and CP/CPPS, and it intends to support a 3-year MAPP Research Network Extension Phase beginning in late FY 2019 that would enable characterization of participants currently enrolled in network studies for an additional 12 months, greatly enriching the network's unique clinical dataset and biological sample archive and allowing for unprecedented assessment of disease progression over time.

An interdisciplinary Specialized Center of Research (SCOR) on Sex and Gender Factors Affecting Women's Health called The Women's Health and Functional Visceral Disorders Center was established through an ORWH program and was co-funded by NIDDK and ORWH.[925] It studied the interplay between gut and brain pathways in irritable bowel syndrome (IBS) and interstitial cystitis/bladder pain syndrome, focusing on sex differences in the development, clinical manifestation, and treatment response in these pain syndromes. One study from the SCOR found that people with IBS, when facing an uncertain threat of pain,

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[919] https://nccih.nih.gov/research/results/spotlight/carpal.
[920] Maeda Y, et al. *Brain* 2017;140(4):914-27. PMID: 28334999.
[921] https://www.mappnetwork.org.
[922] Stephens-Shields AJ, et al. *J Urol* 2016;196(5):1450-5. PMID: 27131464.
[923] Lai HH, et al. *J Urol* 2017;198(3):622-31. PMID: 28373134.
[924] Kutch JJ, et al. *Pain* 2017;158(6):1069-82. PMID: 28328579.
[925] https://projectreporter.nih.gov/project_info_description.cfm?aid=6669104&icde=52906423&ddparam=&ddvalue=&ddsub=&cr=29&csb=default&cs=ASC&pball=.

engage brain regions involved in threat appraisal and emotion more than healthy people do.[926] The results from this study strengthen the understanding of the cause of IBS, which appears to involve signals flowing in both directions between the brain and the gut.

Clarifying underlying causes of symptoms in chronic pain conditions is helpful for clinical treatment. NIDDK-supported researchers examined possible autonomic nervous system (ANS) contributions to chronic pelvic pain conditions in women. Nerves that are part of the ANS regulate unconscious activities, such as heart rate, blood pressure, digestion, and bladder function; if ANS nerves malfunction or become damaged, however, a person can experience such symptoms as dizziness, increased or decreased sweating, and problems with urination. Overall and in combination with earlier research, the study results suggest that women with chronic pelvic pain (IC/BPS and/or myofascial pelvic pain), particularly women with IC/BPS, may have systemic neural changes rather than nerve problems restricted to, for example, the bladder.[927] The indicator of this systemic change, called vagal tone withdrawal, can potentially be addressed therapeutically.

Veterans are in pain, according to an analysis of the 2010–2014 NHIS, a large survey conducted annually by CDC's National Center for Health Statistics. The analysis by NCCIH found that almost two-thirds of U.S. military veterans say they are in pain, and 9.1 percent say their pain is severe.[928] Veterans were also more likely than nonveterans to suffer from a range of painful health conditions, such as back and joint pain, and to classify their pain as severe.

In a study of veterans experiencing chronic pain, an online symptom tracker was developed and used by patients prior to treatment in specialty community pain clinics to record patient-reported symptoms. The study found that a significant number of veterans reported symptoms of posttraumatic stress disorder (PTSD), with a greater number of reported PTSD symptoms associated with poorer chronic pain treatment outcomes.[929] Even a report of one of the four symptom areas of PTSD was associated with poorer outcomes. This study is significant because it reveals an important area for clinicians to address when treating veterans with chronic pain.

[926] Hong JY, et al. *Neurogastroenterol Motil* 2016;28(1):127-38. PMID: 26526698.
[927] Chelimsky G, et al. *J Urol* 2016;196(2):429-34. PMID: 27026035.
[928] Nahin RL. *J Pain* 2017;18(3):247-54. PMID: 27884688.
[929] Langford DJ, et al. *J Pain* 2018;19(5):506-14. PMID: 29307748.

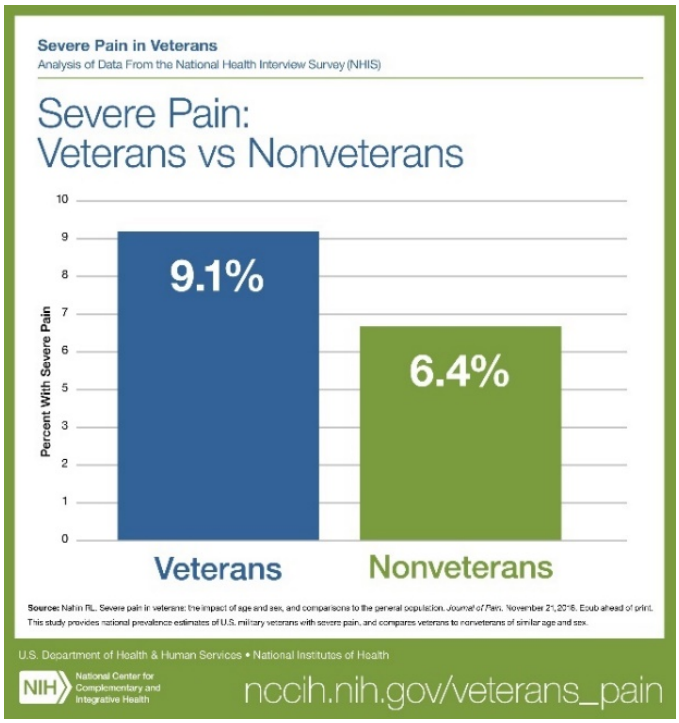

Figure 60. "Severe Pain: Veterans vs Nonveterans": Infographic. Credit: NCCIH.

Improving Treatment and Prevention

NCCIH is leading an interagency partnership involving HHS, DoD, and VA to fund a multi-project research program focusing on nondrug approaches for pain management in military personnel, veterans, and their families. This initiative, called the NIH-DoD-VA Pain Management Collaboratory,[930] is focused on developing, implementing, and testing cost-effective, large-scale, real-world research on nonpharmacologic approaches for pain management and related conditions in military and veteran health care delivery organizations. The Collaboratory currently funds 11 pragmatic clinical trial research project grants and a resource coordinating center, totaling approximately $81 million over 6 years, with the NCCIH contributing more than half of these funds.[931,932] The studies will not only show if these approaches are effective for pain management, but also how they can be integrated into a health care system. The studies also may lead to new pain management practices within the DoD and VA and support the use of nonpharmacologic approaches for pain management in the general population.

[930] https://painmanagementcollaboratory.org.
[931] https://grants.nih.gov/grants/guide/rfa-files/rfa-at-17-001.html.
[932] https://grants.nih.gov/grants/guide/rfa-files/rfa-at-17-002.html.

Figure 61. "Fighting pain in the U.S. military and veterans": Infographic. Credit: NCCIH.

Up to 87 percent of all people who undergo amputation experience phantom limb pain, painful sensations that seem to be coming from the part of the limb that was removed. Unfortunately, many of these patients do not respond to traditional pain treatments and have to endure this suffering throughout their lives. A technique called repetitive transcranial magnetic stimulation (rTMS) provides a simple, safe, noninvasive means to locally stimulate brain circuitry and promote therapeutic outcomes. NICHD-supported researchers conducted a clinical trial of 54 land-mine amputees, finding that traumatic amputees with phantom limb pain treated with rTMS had significantly reduced pain for up to 15 days after treatment, whereas amputees treated with a sham version did not have reduced pain.[933] The effect did not persist to 30 days after treatment, but no adverse effects were noted, indicating that rTMS has potential as a safe, effective, and noninvasive treatment to reduce phantom limb pain for amputees.

Researchers have shown that pain-induced changes in the rat brain's opioid receptor system may explain the limited effectiveness of opioid therapy in chronic pain and may play a role in the depression that often accompanies it.[934] An NCCIH-funded study performed cross-sectional PET imaging on the brains of 17 rats that had undergone surgery to produce a nerve injury that causes chronic pain and 17 rats that had

[933] Malavera A, et al. *J Pain* 2016;17(8):911-8. PMID: 27260638.
[934] Thompson SJ, et al. *Pain* 2018;159(9):1856-66. PMID: 29794614.

undergone sham surgery—a similar procedure that does not cause chronic pain. Three months later, the availability of opioid receptors had decreased in multiple regions of the brain in the nerve-injured rats, but no changes had occurred in the sham-surgery rats.[935] These findings clearly show the impact of chronic pain on the brain and its relation to depression.

American adults who use complementary health approaches to treat or manage pain spent an estimated $14.9 billion out-of-pocket on these approaches, according to the 2007 NHIS.[936] This amount accounts for 20 percent to 25 percent of all out-of-pocket spending to treat or manage pain, including complementary and conventional care. The four pain conditions with the highest estimated out-of-pocket spending for complementary approaches ($13.7 billion total) were back pain, neck pain, joint pain, and arthritis.

The NIDDK-supported IBS Outcome Study (IBSOS) is a multicenter, placebo-controlled randomized clinical trial with the goal of determining whether self-administered cognitive behavioral therapy (CBT) is as helpful as standard therapy with a therapist in reducing IBS symptoms and overall burden. Not only has CBT been found to be effective, but one IBSOS study from 2018 showed that a primarily home-based CBT regimen (including learning how to relieve stress and pain) is just as effective as standard CBT, which is similar but more expensive and strictly clinic based.[937] Home-based CBT was also found to be more effective than an education-only approach. This suggests that the primarily home-based CBT provides a more low-cost, time-efficient, and accessible alternative to the standard CBT.

For patients with painful knee osteoarthritis, tai chi was as helpful as physical therapy in reducing pain and improving physical functioning, according to a study partially funded by NCCIH.[938] In this study, 204 patients aged 40 years or older who had knee pain and proven osteoarthritis of the knee were randomly assigned to standardized group tai chi training (two 1-hour sessions each week for 12 weeks) or standard physical therapy (two 30-minute sessions per week for 6 weeks, followed by 6 additional weeks of home-based exercises). Patients in the two groups had similar decreases in pain and improvements in physical functioning after 12 weeks, and the benefits were maintained for the 52 weeks of the study. Patients in the tai chi group had more improvement in depression symptoms and quality of life than those in the physical therapy group.

For adults with chronic low-back pain, two mind and body practices—mindfulness-based stress reduction (MBSR) and CBT—resulted in greater improvement in pain and reduced functional limitation, compared to usual care.[939] The randomized study was funded by NCCIH and found that among adults with chronic low-back pain, treatment with MBSR or CBT, compared with usual care, resulted in greater improvement in back pain and functional limitations at 26 weeks, with no significant differences in outcomes between MBSR and CBT. These findings suggest that MBSR may be an effective treatment option for patients with chronic low-back pain.

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[935] https://nccih.nih.gov/news/press/opioids-may-not-always-work-well-chronic-pain.
[936] Nahin RL, et al. *J Pain* 2015;16(11):1147-62. PMID: 26320946.
[937] Lackner JM, et al. *Gastroenterology* 2018;155(1):47-57. PMID: 29702118.
[938] Wang C, et al. *Ann Intern Med* 2016;165(2):77-86. PMID: 27183035.
[939] Cherkin DC, et al. *JAMA* 2016;315(12):1240-9. PMID: 27002445.

Results from a study funded in part by NCCIH demonstrate that mindfulness meditation does not rely on the endogenous opioid activity to reduce pain, which is an important consideration for using meditation to treat chronic pain. In the study, researchers recorded pain reports in 78 healthy adults during meditation or a non-meditation control condition in response to painful heat stimuli and intravenous administration of the opioid antagonist naloxone (a drug that blocks the transmission of opioid activity) or placebo saline. The researchers found that participants who meditated during naloxone administration or saline administration had significantly lower pain intensity and unpleasantness ratings, compared to the related control group.[940] These findings demonstrate that mindfulness meditation reduces pain independently of opioid neurotransmitter mechanisms. The results suggest that combining mindfulness-based and pharmacologic/nonpharmacologic pain-relieving approaches that rely on opioid signaling may be effective in treating pain.

Newly diagnosed lung cancer patients who received an early integrated palliative and oncology care intervention reported improved quality of life and less depression in comparison with lung cancer patients receiving usual care.[941] However, patients with non-colorectal gastrointestinal cancer receiving either the intervention or usual care reported improvements in mood and quality of life. The difference between the patient groups may be associated with gastrointestinal cancer patients' spending more time in hospitals prior to cancer diagnosis. Patients receiving the intervention were more likely to have discussed their preferences in end-of-life care with clinicians and to report that knowing their prognoses was helpful in decision-making. These findings indicate a significant positive impact of discussions with palliative care clinicians on patients with incurable cancer.

Cancer patients with depressive symptoms who participated in two RCTs of early palliative care versus delayed or usual care were found to benefit significantly from early palliative care.[942] Those patients with higher levels of depressive symptoms were found to receive the greatest benefit and had lower mortality rates. Further research is needed to determine what mechanisms are responsible for these changes.

An NINR funding opportunity titled *Palliative Care Needs of Individuals with Rare Advanced Diseases and Their Family Caregivers* seeks to expand knowledge and increase the evidence base for palliative care in advanced rare diseases, including rare cancers, and to improve physical and psychosocial well-being and quality of life among seriously ill individuals and their family caregivers.[943] Another NINR FOA seeks to advance research that will improve and increase the use of evidence-based interventions in end-of-life and palliative care for American Indians and Alaska Natives (AI/AN) with advanced illness and their families and communities.[944]

Patients with chronic conditions often present with a symptom cluster (e.g., pain, fatigue, sleep disturbance); if left undertreated, these symptoms add to patients' distress and functional impairment. The purpose of another NINR funding initiative is to encourage research on symptom cluster

[940] Zeidan F, et al. *J Neurosci* 2016;36(11):3391-7. PMID: 26985045.
[941] Temel JS, et al. *J Clin Oncol* 2017;35(8):834-41. PMID: 28029308.
[942] Prescott AT, et al. *Health Psychol* 2017;36(12):1140-6. PMID: 29048177.
[943] https://grants.nih.gov/grants/guide/pa-files/PA-17-018.html.
[944] https://grants.nih.gov/grants/guide/pa-files/PAR-19-057.html.

characterization that has potential to inform treatment and interventions that improve functional outcomes and quality of life in patients with chronic conditions.[945]

NICHD recently released a FOA on *Safety and Outcome Measures of Pain Medications Used in Children and Pregnant Women*. This FOA aims to promote preclinical, translational, clinical, and epidemiological research on pain medications' use in children or pregnant women and to develop effective approaches to evaluate child and maternal outcomes of pain medication treatments.[946]

A study examining California Medicaid claims data over a period of 4 years found limited pediatric hospice care utilization among children who died during that time period. On average, only 10 percent of all children who died were enrolled in hospice care, with an average stay of 3 days.[947] Although almost half of child mortalities in the sample had multiple complex chronic conditions (MCCCs), only a small percentage used hospice care. Children with MCCCs who utilized hospice care were enrolled for significantly longer periods of time than the 3-day average. More research is needed to determine if any obstacles exist to pediatric palliative care access, especially for children with MCCCs.

Data from Medicaid claims were used to determine factors that influence the decision to use hospice care for infants with life-threatening health conditions.[948] Infant girls and infants born with congenital anomalies were more likely to be enrolled in hospice care and to use that care for a longer period of time than infants with other health conditions. Infants with cardiovascular and respiratory conditions were less likely to be in hospice. These findings are important for clinicians to be aware of because they affect how clinicians approach families with infants who have life-threatening conditions and the information they provide to these families.

A study investigated the role that families may play in the experience of symptoms among adolescents living with HIV at the end of life (e.g., pain, fatigue, trouble sleeping/breathing), and how important it is for families to understand the adolescent's treatment preferences.[949] The study showed that the more that families understand adolescent's end-of-life treatment preferences, the less likely adolescents are to suffer symptoms related to HIV.

The Palliative Care Research Cooperative (PCRC) Group is the only research network of its kind in the field of end-of-life and palliative care science and the only federally funded program that serves to expand much-needed research capacity, training, and resources in palliative care science.[950] The PCRC consists of 501 interdisciplinary members from more than 170 different locations, including six international sites that work collaboratively to conduct high-quality, impactful research in the area of palliative care. In 2018, NINR awarded a continuation of the PCRC to support palliative care research and resource activities. By

[945] https://grants.nih.gov/grants/guide/pa-files/PA-17-461.html.
[946] https://grants.nih.gov/grants/guide/pa-files/PA-18-038.html.
[947] Lindley LC. *J Palliat Med* 2017;20(3):241-6. PMID: 27797636.
[948] Lindley LC and Newnam KM. *J Pediatr Health Care* 2017;31(1):96-103. PMID: 27245660.
[949] Lyon ME, et al. *Pediatrics* 2018;142(5). pii: e20173869. PMID: 30341154.
[950] https://palliativecareresearch.org.

addressing the objectives of this new award, the PCRC is expected to further develop areas of specific scientific growth through the continuation and expansion of its centers and research cores.

In FY 2018, NINR and the NLM's MedlinePlus® teamed up to offer a text message campaign for those living with serious illnesses and their families.[951] The campaign launched on February 5, 2018, and offers weekly messages about palliative care in English and Spanish. Palliative care's primary purpose is to relieve the pain and other symptoms associated with serious illnesses and improve quality of life. The text messages provide information about what palliative care is, the benefits of palliative care, and how to manage the symptoms of a serious illness. Messages include palliative care information for both adult and pediatric patients and their families.

NINR designed an evidence-based campaign in 2014 to raise awareness of pediatric palliative care and to facilitate conversations about palliative care between health care providers, children living with a serious illness, and their families. In 2018, the Palliative Care: Conversations Matter® Pediatric Palliative Care Tear-Off Pad was updated based on suggestions made by health care providers.[952] The tear-off pads encourage providers to have discussions with patients and their families by providing answers to common questions about palliative care and offering resources to support conversations. The pads contain customizable patient education sheets that can be filled out during patient visits. The tear-off pad is available in English and Spanish.

More than 90 percent of infants hospitalized in the intensive care unit undergo multiple painful procedures. Dexmedetomidine, which is approved for use in adults for sedation in intensive care units or during procedures, is being used regularly for sedation in infants undergoing painful procedures, even though the drug label does not support use in infants and young children. Researchers supported by NICHD, NIAID, NHLBI, NCATS, and the NIH Office of the Director aimed to understand how different doses affect the amount of dexmedetomidine in the blood, how long it takes the drug to clear from an infant's body, and whether different doses are needed for different ages. After collecting blood samples from 20 infants receiving this pain-controlling medication, the researchers showed that the drug was processed by younger infants much more slowly than older infants.[953] Likewise, children recovering from cardiac surgery cleared the drug approximately 40 percent slower than other infants. The study findings suggest that younger infants or those receiving the drug for pain control after cardiac surgery may respond to lower doses and still achieve adequate pain control.

Endometriosis occurs when tissue similar to the lining of the uterus grows in other places in the body, which primarily causes pain and infertility. FDA recently approved elagolix for pain associated with endometriosis;[954] elagolix was partly developed through an NICHD-funded small business award.

Vulvodynia is a relatively common chronic pain syndrome in women characterized by persistent or recurrent pain in the genital area in the absence of infection or another specific cause. Gabapentin (brand

[951] https://magazine.medlineplus.gov/article/pediatric-palliative-care-resources-for-you.
[952] https://www.ninr.nih.gov/sites/files/docs/NINR_Palliative_Care_ENG_Tear_Pad_508c.pdf.
[953] Greenberg RG, et al. *J Clin Pharmacol* 2017;57(9):1174-82. PMID: 28444697.
[954] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210450Orig1s000TOC.cfm.

name Neurontin), a drug approved for control of seizures or nerve pain associated with shingles infections, is commonly prescribed to treat vulvodynia pain. RCTs have found gabapentin to be effective in controlling various neuropathic (nerve pain) conditions; however, NICHD supported an 18-week, multicenter RCT of time-release gabapentin that found gabapentin was no more effective in treating vulvodynia pain than a placebo.[955]

Provoked vestibulodynia (PVD) is the most common subset of vulvodynia, in which women experience pain of unexplained origin when touched (e.g., during a medical exam) in the area at the entrance to the vagina. Fibromyalgia is associated with widespread skeletal-muscular pain, provoked at many points on the body. Many people with chronic pain have more than one pain-related condition, and many women may have both PVD and fibromyalgia. In a recent study of PVD, researchers found that for women who have both PVD and fibromyalgia, the "provoked" pain in PVD is more severe, compared with women who have just PVD.[956] The results suggest that women with PVD and fibromyalgia may find greater benefit from early interventions, including pelvic floor physical therapy, than women with PVD only.

Following cesarean delivery, the most common major surgical procedure in the U.S., 10 to 15 prescribed opioid tablets per patient (13 to 20 million tablets in total) go unused. A study supported by NICHD found that, compared to women who received the standard amount of opioids after a cesarean section (30 tablets of 5 mg oxycodone), women who received an individualized prescription for opioids (12–16 tablets, based on their use in the hospital before discharge) used the same percent, but only half the number of tablets, suggesting that individualized opioid prescribing based on inpatient use reduces the number of unused oxycodone tablets, compared with standard prescribing.[957]

Supported by NICHD, researchers studied the effects of fentanyl and midazolam, two drugs that are often used for pain relief or sedation in children with traumatic brain injury (TBI). The researchers looked at data from 31 patients with severe TBI up to 18 years of age with an episode of increased pressure in the brain, examining measurements of brain pressure and blood flow within the skull before, during, and after the patients received either or both drugs. In many cases, the drugs increased pressure within the skull.[958] These findings suggest that a common practice in intensive care units to treat severe TBI may be not only ineffective but also damaging to blood flow in the brain.

Cystic Fibrosis

Cystic fibrosis (CF) is an inherited disease of the secretory glands, which include glands that make mucus and sweat. People who have CF inherit two faulty genes for the disease—one from each parent. The parents likely do not have the disease themselves. CF mainly affects the lungs, pancreas, liver, intestines, sinuses, and sex organs. It causes a person's mucus to become so thick and sticky that the mucus builds up in the lungs and blocks the airways. This buildup of mucus makes it easy for bacteria to grow, leading

[955] Brown CS, et al. *Obstet Gynecol* 2018;131(6):1000-7. PMID: 29742655.
[956] Phillips N, et al. *Am J Obstet Gynecol* 2016;215(6):751.e1-751.e5. PMID: 27377821.
[957] Osmundson SS, et al. *Obstet Gynecol* 2018;132(3):624-30. PMID: 30095773.
[958] Welch TP, et al. *Crit Care Med* 2016;44(4):809-18. PMID: 26757162.

to repeated, serious lung infections. Over time, these infections can severely damage the lungs. Mucus also can block tubes, or ducts, in the pancreas. As a result, the digestive enzymes that the pancreas produces cannot reach the small intestine, causing vitamin deficiency and malnutrition.[959]

CF affects more than 30,000 Americans across all gender, racial, and ethnic groups. However, the disease is most common among Whites of Northern European descent. More than 10 million Americans are carriers of a faulty CF gene, although many of them do not know it.

Understanding Prevalence, Risk Factors, and Underlying Biology

NIH research on CF is varied, ranging from basic to clinical research. For example, in September 2017, NHLBI released a new funding announcement, *The Impact of the Microenvironment on Lung Progenitor Cell Function*.[960] Funded researchers are conducting basic science studies on environmental cues that influence lung cell development and cellular responses to injury and disease. Studies of how the progenitor cell microenvironment changes in CF have the potential to inform future therapeutic strategies.

Newborn screening programs help identify infants who are at risk for certain diseases, allowing for early intervention and treatments. NICHD-funded researchers reported a faster and cheaper screening test for CF.[961] Their assay, called Cfseq, allows a comprehensive analysis of dried blood spots to identify mutations in the genes involved in CF.

Other NIH-funded studies aim to discover the underlying biology of CF. Pathogens and foreign particles that enter the lungs are normally cleared away by a protective mucus layer, a process that is often disrupted in CF. The mucus layer is primarily composed of two secreted mucin proteins, MUC5B and MUCBAC. Researchers found that these mucins assemble into distinct thread-like and sheet-like structures, respectively, which likely enable efficient capture and clearance of foreign bodies in the lungs.[962] In CF, these structural features of mucins were altered, which likely contributes to impaired clearance and disease pathogenesis.

In CF, the mucus that normally helps protect the lungs and clear away debris becomes thicker and less fluid and can clog the airways. Another NHLBI-funded study discovered that when mucins are released into a normal lung environment, they unfold into a linear form, but this unfolding is inhibited in the CF airway because of airway surface dehydration.[963]

Researchers found that lower acidity of lungs in mice with CF accounts for their greater resistance to infection and lower mucus viscosity, compared to people with CF.[964] They also found that the transporter

[959] https://www.nhlbi.nih.gov/health/health-topics/topics/cf.
[960] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-022.html.
[961] Lefterova MI, et al. *J Mol Diagn* 2016;18(2):267-82. PMID: 26847993.
[962] Ostedgaard LS, et al. *Proc Natl Acad Sci USA* 2017;114(26):6842-7. PMID: 28607090.
[963] Abdullah LH, et al. *JCI Insight* 2017;2(6):e89752. PMID: 28352653.
[964] Shah VS, et al. *Science* 2016;351(6272):503-7. PMID: 26823428.

protein ATP12A promotes acidity in human lungs, but that ATP12A expression is low in the mouse airway. This suggests that strategies to buffer airway surface liquid or to reduce acidification by inhibiting ATP12A have the potential to reduce infections in people with CF. These findings help explain why CF mice are protected from infection and nominate ATP12A as a potential therapeutic target for CF.

Improving Treatment and Prevention

In CF, the lung airway surface liquid becomes acidic, which inhibits airway defenses and can promote bacterial infection. Researchers conducted a proof-of-concept study in an animal model using aerosolized tromethamine, an FDA-approved drug for metabolic acidosis, to neutralize the acidified airway surface liquid.[965] They found that tromethamine alone and in conjunction with hypertonic saline enhanced bacterial killing, suggesting a possible therapeutic application in CF.

CF is a single-gene disease, caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. NHLBI is investing in research to develop molecular therapies, including drugs to compensate for *CFTR* mutations and gene editing to repair them. To identify sites within the *CFTR* gene that could be targeted for therapy, NHLBI-funded researchers studied the CFTR protein in zebrafish, which is 55 percent identical to human CFTR. They examined the atomic structure of the protein and how genetic changes to the protein's structure affect its function.[966] These findings can be used to design drugs and gene-editing approaches, which then can be tested in zebrafish carrying *CFTR* mutations.

Animal models of CF are critical for better understanding the disease process and developing new therapies. NHLBI-funded researchers implemented a new strategy to select adeno-associated virus (AAV) vectors best suited for gene therapy in a swine model of CF.[967] Using this method, the researchers were able to administer functional CFTR to the airways in the swine model and improve several physiological markers of lung disease.

NHLBI supported a workshop in 2018, *Advancing Gene Editing Technologies for the Treatment of Cystic Fibrosis Lung Disease*, to develop a strategic research agenda for NHLBI on this topic.[968] Among the recommendations are to develop and optimize gene-editing technologies for the *CFTR* gene locus, improve understanding of the basic pathobiology of CF, develop better model systems that can more accurately evaluate gene-editing safety and efficacy, and develop new technologies to specifically and accurately deliver gene-editing therapies to the lungs.

[965] Abou Alaiwa MH, et al. *JCI Insight* 2016;1(8). pii: 87535. PMID: 27390778.
[966] Zhang Z and Chen J. *Cell* 2016;167(6):1586-97.e9. PMID: 27912062.
[967] Steines B, et al. *JCI Insight* 2016;1(14):e88728. PMID: 27699238.
[968] https://www.nhlbi.nih.gov/events/2018/nhlbicff-workshop-advancing-gene-editing-technologies-treatment-cystic-fibrosis-lung.

Craniofacial Diseases

Oral or dental diseases have the potential to affect all Americans. From cavities to periodontal (gum) diseases, chronic dental diseases can affect health and well-being. CDC estimates that 47.2 percent of adults age 30 years and older have some form of periodontal disease and that tooth decay is the most common chronic disease among children ages 6–19 years—four times more common than asthma among 14- to 17-year-olds. NIH has a research portfolio dedicated to understanding and treating chronic dental diseases.

NIDCR is the federal government's lead agency for scientific research on dental, oral, and craniofacial health and disease. However, other NIH ICs also contribute to NIH's portfolio in this area, where the research aligns with their mission.

NIDCR's National Dental Practice Based Research Network aims to answer questions of everyday relevance to dental practitioners and their patients.[969] Over the past 14 years, more than 7,000 dental practitioners and 60,000 patients in all 50 states have participated in clinical research studies. Study findings have guided practitioners in identifying risk factors for the development of oral conditions, led to more effective treatments and preventive approaches, and provided evidence to better inform oral health treatment decisions. Building on the momentum of previous investments, the National Dental Practice Based Research Network will add a Specialty Node to recruit and engage dental specialists, as well as a Patient Population Node to link practitioners with specific practices and patients.[970–972]

NIDCR also co-leads the National Academy of Medicine Forum on Regenerative Medicine, which brings together experts from diverse backgrounds and organizations to overcome challenges and accelerate development of new cures. This public–private partnership has supported multiple workshops to develop and share research strategies for the regenerative medicine community. These strategies include determining which stem cell types work best for developing therapies, as well as optimizing the manufacturing assembly line to generate safe and high-quality stem cells. By providing best practices and encouraging collaboration, the forum is speeding up the translation of regenerative medicine therapies into the clinical pipeline and onto the market.[973]

In 2018, the U.S. Surgeon General commissioned NIDCR to lead the production of a *Report on Oral Health in America,* to be released in 2020, the 20th anniversary of the first Oral Health in America report.[974] NIDCR is working with the U.S. Public Health Service's Oral Health Coordinating Committee, CDC, and other stakeholders to reexamine the state of oral health in Americans across the lifespan. The report will identify

[969] http://www.nationaldentalpbrn.org/.
[970] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-19-001.html.
[971] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-19-002.html.
[972] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-19-006.html.
[973] http://www.nationalacademies.org/hmd/Activities/Research/RegenerativeMedicine.aspx.
[974] https://www.nidcr.nih.gov/news-events/2020-surgeon-generals-report-oral-health.

opportunities and obstacles in advancing dental, oral, and craniofacial health and serve as a vital resource by establishing guidelines for research priorities and public policy.

NIDCR has played a leading role in advancing the scientific development of autotherapies, treatments based on the body's natural ability to heal and protect itself by repairing and regenerating tissues, resolving inflammation, triggering immune responses to overcome disease, and restoring a natural microbial balance. In 2018, NIDCR hosted a symposium that brought together leading-edge researchers in this field to present the latest science and discuss gaps, challenges, and opportunities for advancing autotherapies research.[975]

NIDCR is supporting research to repair, regenerate, and restore the function of damaged salivary glands that result in chronic dry mouth. IRP scientists have developed a gene therapy treatment using an AAV vector to deliver a water channel called human aquaporin-1 into the salivary glands of individuals with chronic dry mouth to restore salivary flow. This promising treatment, which restored salivary gland function in mice, is currently being tested in patients with radiation-induced chronic dry mouth in a clinical trial at the NIH CC.[976]

Periodontal disease, the result of chronic infection and inflammation of tissues that surround and support the teeth, is associated with other serious health conditions, such as heart disease and type 2 diabetes. NIDCR-supported researchers analyzed data from a large clinical study of older American veterans with periodontal disease and type 2 diabetes and found that regular treatments for periodontal disease were associated with long-term improvements in blood sugar levels. This study demonstrates that oral health care may benefit overall health.[977]

The mucosal tissues that line the inside of the mouth, digestive tract, nose, and other organs keeps people healthy by forming both a physical and an immune system barrier against invading microbes. NIDCR intramural researchers discovered that mechanical stimulation from chewing activates specialized immune cells called T helper cells (Th17) in the oral mucosa. The oral Th17 response ramps up the body's protective immunity, but it may also increase inflammation in the gums and contribute to periodontal disease. Future studies of Th17 could further compare these two different outcomes and try to reduce or prevent the contribution of Th17 cells to periodontal soft tissue and bone loss, while retaining its protective effects on oral immunity.[978]

The mouth is home to a diverse community of microbial species, including *Streptococcus mutans*, the primary bacterium that causes dental caries. Distinct *S. mutans* subtypes are distinguished from one another by small molecular differences in their genetic makeup. NIDCR-supported investigators analyzed these genetic differences and found that children have anywhere between one and nine of these subtypes in their mouths and that children infected with multiple *S. mutans* subtypes were more than twice as likely

[975] https://nidcr2030.ideascale.com/community-library/accounts/93/931091/Public/AutotherapiesSummary-508.pdf.
[976] Lai Z, et al. *Proc Natl Acad Sci USA*. 2016;113(20):5694-9. PMID: 27140635.
[977] Merchant AT, et al. *J Dent Res* 2016;95(4):408-15. PMID: 26701348.
[978] Dutzan N, et al. *Immunity*. 2017;46(1):133-47. PMID: 28087239.

to have dental caries. Uncovering the impact of the genetic diversity of bacteria on oral health could lead to improved risk assessment and prevention strategies for dental caries.[979]

Since regular tooth brushing using fluoridated toothpaste is a well-established practice for maintaining good oral health, more effective behavioral and technological approaches to improve tooth brushing behavior will positively impact oral health. One group of NIDCR-supported researchers used a new behavioral measure called the Tooth Brushing Observation System to characterize parent and child toothbrushing behavior. They found that parent-led toothbrushing—as opposed to independent child toothbrushing—was associated with reduced caries and gingivitis, emphasizing the important roles of parents and caregiver supervision in improving oral health in children.[980]

Nausea and vomiting in early pregnancy, commonly referred to as morning sickness, occurs in up to 80 percent of pregnancies. Contrary to earlier studies, an analysis of more than 1.8 million pregnancies, in which 88,000 had at least one prescription for the anti-nausea drug ondansetron, found no increased risk for newborn heart malformations and only a slightly increased risk for cleft lip and palate.[981,982]

Xenopus embryos and tadpoles are used to study the development of the head and face. For many years, scientists have relied on the reference Normal Table of *Xenopus laevis*, but some notable stages of development were missing. To help researchers and students, a group of NICHD-supported scientists filled in the missing gaps by creating 27 high-quality illustrations to provide standardized images of different stages of embryonic development. Known as the *Zahn drawings*, these images are publicly available and will help researchers efficiently and accurately identify and communicate stage-specific experimental data.[983] The Zahn drawings will be permanently hosted at Xenbase[984] and are freely available for noncommercial use.

Diabetes

Diabetes, a disease that occurs when a person's blood glucose (BG) is too high, is the seventh leading cause of death in the U.S. BG is the body's main source of energy and comes from food. Insulin, a hormone made by the pancreas, helps glucose from food get into the cells to be used for energy. Sometimes the body does not make enough, or any, insulin or does not use insulin well. Glucose then stays in the blood and does not reach the cells. More than 30 million Americans suffer from diabetes, and another 84 million have a condition called prediabetes, which puts them at risk for type 2 diabetes.[985] Diabetes has serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations.

[979] Momeni SS, et al. *J Microbiol Methods*. 2016;128:108-17. PMID: 27432341.
[980] Collett BR, et al. *Int J Paediatr Dent* 2016;26(3):184-92. PMID: 26148197.
[981] https://www.nichd.nih.gov/newsroom/news/122018-anti-nausea.
[982] Huybrechts KF, et al. *JAMA* 201;320(23):2429-37. PMID: 30561479.
[983] Zahn N, et al. *Development* 2017;144(15):2708-13. PMID: 28765211.
[984] http://www.xenbase.org/entry/.
[985] https://www.cdc.gov/diabetes/basics/diabetes.html.

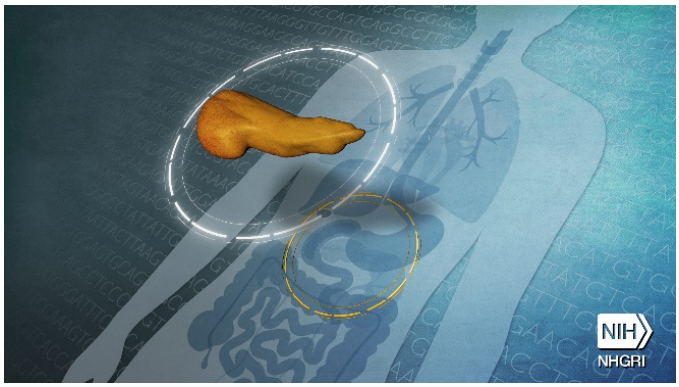

Figure 62. A representative image of the pancreas. Beta cells in the pancreas produces insulin, lack of which can cause type 2 diabetes. Credit: Ernesto Del Aguila III, NHGRI.

The most common types of diabetes are type 1, type 2, and gestational diabetes mellitus (GDM). In people with type 1 diabetes, the body does not make insulin; the immune system attacks and destroys the beta cells in the pancreas that make insulin. Type 1 diabetes is usually diagnosed in children and young adults, although it can appear at any age. People with type 1 diabetes need to take insulin every day to stay alive. In people with type 2 diabetes, the most common type of diabetes, the body does not make or use insulin well. People can develop type 2 diabetes at any age, even during childhood. However, this type of diabetes occurs most often in middle-aged and older people. GDM develops in some women when they are pregnant and needs to be managed to help prevent complications for the mother and offspring during delivery. GDM usually resolves with delivery, but women who have had GDM have a greater chance of developing type 2 diabetes later in life.

Given the prevalence of diabetes and the seriousness of its potential health consequences, NIH invests in diabetes research that includes understanding how and why people develop diabetes, who is at risk, and how diabetes can be treated and prevented.

Figure 63. A finger stick helps patients with diabetes take control of their blood sugar levels. Credit: Darryl Leja, NHGRI.

Understanding Prevalence, Risk Factors, and Underlying Biology

Search for Diabetes in Youth (SEARCH),[986] an ongoing study led by CDC and NIDDK, revealed that from 2002 to 2012, the annual increase in type 1 diabetes diagnosis among U.S. youth was 1.8 percent, and the annual increase in type 2 diabetes diagnosis was 4.8 percent.[987] However, the increase varied across racial and ethnic groups: A significant annual increase was found in type 2 diabetes diagnoses among all racial and ethnic groups except non-Hispanic Whites, and type 1 diabetes incidence increased significantly more in Hispanic youths than in non-Hispanic White youths. SEARCH investigators also reported that by about age 21, approximately 32 percent of SEARCH study participants with type 1 diabetes and 72 percent of participants with type 2 diabetes had at least one complication from diabetes or were at high risk for a complication.[988]

With contributions from leading diabetes experts from around the world, NIDDK completed the third edition of an online resource designed to be a preeminent source for crucial scientific information on diabetes and its complications: *Diabetes in America, 3rd Edition*.[989] An assessment of epidemiologic, public health, clinical, and clinical trial data on diabetes and its complications in the U.S., this resource describes data and trends, disparities, and prevention and medical care for diabetes, including outlining major diabetes research findings. It also describes well-known complications of diabetes—such as heart, eye, kidney, and nerve diseases—while showing the connection between diabetes and other serious conditions that people may not associate with diabetes, such as dementia, cancer, hearing loss, osteoarthritis, and bone fractures.

Research newly funded by NIEHS includes a project evaluating the contributions of mixtures of environmental chemicals (e.g., polychlorinated biphenyls [PCBs], bisphenol-A, phthalates, and arsenic) to later development of obesity, type 2 diabetes, and metabolic syndrome in the Study of Women's Health Across the Nation (SWAN), a multisite, multiethnic cohort of midlife women who are at increased metabolic risk.[990] In fact, one study found that in a pregnancy cohort of women, higher exposure to mono-ethyl phthalate may be associated with excessive gestational weight gain and impaired glucose tolerance.[991] Another study in mice found that inhaled ozone was observed to induce oxidative stress, inflammation in adipose tissue, and insulin resistance.[992] NIEHS-supported researchers are also examining the role of PFAS, a group of man-made chemicals, in metabolic diseases in children.[993] They hypothesize that PFAS-induced inflammation may be involved in metabolic abnormalities. The researchers are examining children in an established birth cohort to explore the associations between age-related PFAS exposure profiles and metabolic abnormalities. NIEHS researchers also analyzed the effect of various

[986] https://searchfordiabetes.org/dspHome.cfm.
[987] Mayer-Davis EJ, et al. *N Engl J Med* 2017;376(15):1419-29. PMID: 28402773.
[988] Dabelea D, et al. *JAMA* 2017;317(8):825-35. PMID: 28245334.
[989] https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/diabetes-in-america-3rd-edition.
[990] https://www.niehs.nih.gov/research/supported/health/obesity/index.cfm.
[991] James-Todd TM, et al. *Environ Int* 2016;96:118-26. PMID: 27649471.
[992] Zhong J, et al. *Inhal Toxicol* 2016;28(9):383-92. PMID: 27240593.
[993] https://www.niehs.nih.gov/research/programs/pfas/index.cfm.

environmental factors on the maintenance and function of pancreatic islets and develop new therapeutic strategies for diabetes.[994]

Type 2 diabetes was once rare in children; now, each year, more than 5,000 new cases of type 2 diabetes are estimated to be diagnosed among U.S. youth younger than age 20. For adults, scientists have identified unique genetic factors that raise the risk of developing type 2 diabetes, such as the *TCF7L2* gene. Researchers supported by NCATS, NICHD, and NIDDK found that a specific variation in this gene was associated with a higher risk of impaired glucose tolerance and type 2 diabetes in adolescents with obesity.[995]

A genetic analysis in Pima Indians of the American Southwest, who have among the highest rates of type 2 diabetes in the world, has identified a rare mutation linked to elevated birth weight that is later associated with higher risk of type 2 diabetes. To understand their unique genetic risk factors, and find ways to help alleviate this health disparity, NIDDK intramural researchers examined the DNA from 7,710 Pima study volunteers, finding that 3.3 percent of the participants had a previously uncharacterized variation in the gene *ABCC8*, which encodes a protein with a key role in regulating insulin secretion.[996] The resulting genetic change (designated R1420H) was similar to known mutations that inactivate *ABCC8* and initially cause the pancreas to release more insulin than is needed but, for unknown reasons, later lead to a decline in insulin production, typically followed by type 2 diabetes.

The Accelerating Medicines Partnership Type 2 Diabetes Program is taking the extensive available data on type 2 diabetes genetics, broadening it, and making it more freely accessible and useful through a knowledge portal that integrates data on more than 200 genetic loci that are known to affect type 2 diabetes risk and how they differ in various populations, including disproportionately affected minorities. The portal incorporates new analytic tools to help researchers and pharmaceutical companies mine the data to identify druggable targets and understand how the genes contribute to health and disease. [997] Awards for augmenting the genetic data and for continuing development of this resource were recently made by NIDDK; the work is also supported by industry through the FNIH.

Because early exposure to complex foreign proteins may increase the risk of type 1 diabetes in genetically susceptible children, researchers tested whether hydrolyzed infant formula, which lacks intact proteins, could decrease the onset of type 1 diabetes. NICHD supported a large international trial,[998] which found that weaning to hydrolyzed, compared with conventional formula, failed to reduce overall incidence of type 1 diabetes.[999] Thus, no evidence supported revising dietary guidelines for at-risk infants.

The Environmental Determinants of Diabetes in the Young (TEDDY) is an NIDDK-led study to identify environmental factors that trigger or protect against type 1 diabetes in genetically susceptible

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[994] Jetten AM. *Cell Mol Life Sci* 2018;75(19):3473-94. PMID: 29779043.
[995] Cropano C, et al. *Diabetes Care* 2017;40(8):1082-9. PMID: 28611053.
[996] Baier LJ, et al. *Diabetes* 2015;64(12):4322-32. PMID: 26246406.
[997] http://www.type2diabetesgenetics.org/.
[998] https://clinicaltrials.gov/ct2/show/NCT00179777.
[999] Writing Group for the TRIGR Study Group, Knip M, et al. *JAMA.* 2018;319(1):38-48. PMID: 29297078.

individuals.[1000] The TEDDY study is currently following more than 6,000 high-risk newborns until they are 15 years of age, collecting dietary and health data as well as stool, blood, and other samples. A significant -omics effort is underway to address questions related to the cause and course of autoimmunity and type 1 diabetes, including metabolomics, proteomics, and studies of the microbiome and virome. For example, researchers from the study have determined that levels of vitamin D and genetic variants in the vitamin D receptor gene may have a combined role in the development of islet autoimmunity in children at high genetic risk for type 1 diabetes.[1001] The researchers found that in children who had a variant in their vitamin D receptor gene, higher childhood vitamin D levels were associated with lower islet autoimmunity. These results highlight how an environmental factor (i.e., vitamin D) interacts with an individual's genetic background to affect health and disease.

GDM is a common pregnancy complication. Women who develop impaired tolerance to glucose (sugar) or GDM during pregnancy are at substantially increased risk for type 2 diabetes in the years following pregnancy. NICHD supports analyses of data from the Diabetes and Women's Health Study,[1002] focused on novel pathways and determinants of progress from GDM to type 2 diabetes. These NICHD intramural researchers reported that taking vitamin D before pregnancy could lower risk of gestational diabetes, based on data from more than 21,000 pregnancies from a longitudinal cohort study of nurses.[1003]

An International Workshop on Gestational Diabetes Treatments was convened August 2–3, 2017, involving obstetricians, maternal–fetal medicine specialists, internists, and endocrinologists with expertise in GDM to address questions and gaps in knowledge regarding the early diagnosis and overall pharmacological management of GDM. A definitive conclusion from the workshop was the need to better understand whether early diagnosis and treatment of maternal dysglycemia would improve the health of the mother and her children. This workshop informed subsequent development of a new, NIDDK-sponsored research funding opportunity, issued in 2018 for FY 2019 funding, that, if successful, will support a clinical research consortium centered on collecting data about maternal BG throughout pregnancy, leveraging such technologies as continuous glucose monitors;[1004,1005] it is anticipated that results from this new initiative could pave the way to clinical trials evaluating new approaches to GDM screening and intervention.

Unless they have a known risk factor, such as obesity, women typically are screened for GDM between 24 and 28 weeks of pregnancy. The hemoglobin HbA1c test is commonly used to diagnose type 2 diabetes but is not currently recommended to diagnose GDM. NICHD intramural researchers compared HbA1c test results at four timepoints during pregnancy in 107 women who later developed GDM and in 214 women who did not develop the condition. Women who went on to develop GDM had higher HbA1c levels, especially in early pregnancy, compared with women without GDM.[1006] These findings suggest that the

[1000] https://teddy.epi.usf.edu/.
[1001] Norris JM, et al. *Diabetes* 2018;67(1):146-54. PMID: 29061729.
[1002] https://www.nichd.nih.gov/about/org/diphr/officebranch/eb/diabetes-women.
[1003] Bao W, et al. *J Diabetes* 201810(5):373-9. PMID: 28976079.
[1004] https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-18-018.html.
[1005] https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-18-019.html.
[1006] Hinkle SN, et al. *Sci Rep* 2018;8(1):12249. PMID: 30116010.

HbA1C test potentially could help identify women at risk for GDM early in pregnancy, when lifestyle changes may be more effective in reducing their risk.

The NIDDK-supported Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study[1007] reported in 2008 a strong linear relationship between increasing maternal BG concentrations (i.e., below concentrations used in the U.S. to diagnose GDM) and adverse neonatal outcomes, although without any clear glucose level threshold; based on these results, many organizations adopted a new definition of GDM.[1008] In 2018, the HAPO Follow Up Study reported a strong relationship between maternal glucose levels during pregnancy that would meet that new GDM definition and subsequent type 2 diabetes in women and obesity in children 10 to 14 years post-delivery; the study did not find a significant relationship between those maternal glucose levels and the combined outcome of overweight and obesity in children.[1009] The results reinforce the importance of trying to prevent GDM in high-risk women and of research that could potentially improve screening and mother/child outcomes.

Women who develop GDM are at higher risk for type 2 diabetes later in life. To assess the impact of subsequent pregnancies, NICHD-supported researchers followed women who had GDM during their pregnancy for 5–10 years after delivery.[1010] The results showed that in women with prior mild GDM, subsequent pregnancies increased the risk of type 2 diabetes, especially if the subsequent pregnancies were also complicated by GDM.[1011]

Untreated diabetic ketoacidosis, a diabetes complication in which the body produces excess blood acids (ketones), can be fatal. Physicians sometimes give children IV fluids to help with treatment, but concerns have arisen that providing too much IV fluid may result in serious brain injury. To evaluate whether IV fluid volume is related to brain injury risk, researchers supported by NICHD studied more than 1,300 children with diabetic ketoacidosis, varying the amount and rate of IV fluid infusion from rapid or gradual and varying the sodium content of the fluid.[1012] The team found no difference in brain injury rates among the treatment regimens: Neither the infusion rate nor the sodium content of the fluid significantly influenced neurological outcomes of the children in the study.[1013]

NICHD intramural researchers are conducting a study on Family Management of Type 1 Diabetes in Youth, which focuses on implementation of behavioral interventions for families of youth with type 1 diabetes and use of a personal trainer to help manage diabetes.[1014]

NIDDK-supported researchers have discovered that human pancreatic islets have four separate subtypes of insulin-producing beta cells, and that islets from people with type 2 diabetes have abnormal

[1007] http://www.hapo.northwestern.edu/.
[1008] Current U.S. criteria for GDM remain essentially the same as pre-HAPO.
[1009] Lowe WL Jr, et al. *JAMA* 2018;320(10):1005-16. PMID: 30208453.
[1010] https://www.nichd.nih.gov/research/supported/mfmu.
[1011] Varner MW, et al. *Obstet Gynecol* 2017;129(2):273-80. PMID: 28079773
[1012] https://www.pecarn.org/.
[1013] Kuppermann N, et al. *N Engl J Med* 2018;378(24):2275-87. PMID: 29897851.
[1014] https://www.nichd.nih.gov/about/org/diphr/officebranch/sbsb/family-management.

percentages of the different subtypes.[1015] Until this discovery, all beta cells were thought to be alike. Importantly, insulin secretion differed among the subtypes, with one subtype being the most glucose responsive and another having the highest basal insulin secretion rate (insulin secretion when glucose levels are low). These observations suggest that differences in the percentages of beta cell subtypes might contribute to the altered timing of insulin secretion and poor glucose control seen in people with type 2 diabetes.

The NIDDK-supported Human Islet Research Network (HIRN) team science program pursued research in beta cell biology and replacement, advancing understanding of how human beta cells are lost in type 1 diabetes and developing innovative strategies for treatment, prevention, and monitoring.[1016] For example, scientists in HIRN (1) developed a new laboratory production method to make large quantities of immature beta cells from the skin cells of people with type 1 diabetes,[1017] (2) identified a novel class of insulin-fused targets that could explain how the type 1 diabetes autoimmune attack is initiated,[1018] and (3) developed a new biomaterial that protects transplanted beta cells and allows them to function without immunosuppression for months in a mouse model of type 1 diabetes.[1019] Additionally, in 2016 HIRN's Human Pancreas Analysis Program began, with the goal of deeply characterizing the human pancreas and its interaction with the immune system to better understand the causes of beta cell loss in type 1 diabetes.

New NIDDK-supported research indicates that a common variation in the gene encoding GLUT2, a protein that allows glucose to move in and out of cells, has a surprising impact on the effectiveness of the first-line antidiabetes medication metformin.[1020] Before treatment, people with two copies of one of the versions of the gene (designated *C*) typically had somewhat worse BG control, as detected by higher levels of HbA1c, a marker for glucose levels. However, these individuals had slightly better (lower) HbA1c when taking a standard dose of metformin than did people with two copies of the other version (*T*) of the GLUT2-encoding gene. This effect was most pronounced in people with obesity but was also seen in others.

The NIDDK Diabetic Foot Consortium was launched in the fall of 2018 to develop a clinical research network that will validate biomarkers for diabetic foot ulcers. Once the clinical research network is established, the consortium's long-term goal is to test new therapies for diabetic foot ulcers through clinical trials at an expanded number of clinical sites.

Improving Treatment and Prevention

Through a community partnership between the UCLA Clinical Translational Science Institute and the Los Angeles County Department of Health Services, NCATS-supported researchers discovered that offering screening in primary care settings for vision loss related to diabetes reduced examination waiting

[1015] Dorrell C, et al. *Nat Commun* 2016;7:11756. PMID: 27399229.
[1016] https://hirnetwork.org/.
[1017] Millman JR, et al. *Nat Commun* 2016;7:11463. PMID: 27163171.
[1018] Delong T, et al. *Science* 2016;351(6274):711-4. PMID: 26912858.
[1019] Vegas AJ, et al. *Nat Med* 2016;22(3):306-11. PMID: 26808346.
[1020] Zhou K, et al. *Nat Genet* 2016;48(9):1055-9. PMID: 27500523.

periods and increased the number of patients served.[1021–1023] Implemented at 15 local primary care centers serving primarily low-income Latino communities, the screenings are maximizing access for this underserved population.

The Glycemia Reduction Approaches in Diabetes: An Effectiveness (GRADE) Study, led by NIDDK with additional support from NHLBI, is comparing long-term benefits and risks of four widely used diabetes drugs in combination with metformin, the most common first-line medication for treating type 2 diabetes.[1024] The study has completed recruitment of more than 5,000 participants and will compare drug effects on glucose levels, adverse effects, diabetes complications, and quality of life over an average of nearly 5 years; an ancillary study is examining how the correlation between HbA1c and average BG differs by racial and ethnic heritage.

The Vitamin D and type 2 diabetes Trial is an NIDDK-supported, randomized, multicenter clinical trial that is testing whether vitamin D supplementation can prevent or delay diabetes in adults who are at high risk for the disease.[1025] The final clinical visits by participants occurred in October 2018, and researchers are analyzing data and will present the results at the American Diabetes Association (ADA) meeting in June 2019.

Damage to the blood vessels of the light-sensitive tissue at the back of the eye (retina), such as diabetic retinopathy (DR) and retinal vein occlusion (RVO), are among the leading causes of vision loss. NEI is funding a promising new clinical trial that will treat patients with RVO. In RVO, the vessels draining blood from retinal tissue become clotted, leading to leaking and bleeding and ultimately starving the neurons of oxygen. The trial will test the safety, feasibility, and efficacy of injecting stem cells derived from the patient's own bone marrow into their eyes.[1026] Additionally, the NEI-funded Diabetic Retinopathy Clinical Research Network (DRCR.net) brings clinicians and patients from across the U.S. and Canada into a single network, so new treatments can be tested for safety and efficacy far faster than through traditional clinical trials. DRCR.net recently conducted its Protocol S trial, which tested panretinal photocoagulation, the standard-of-care since the 1970s, against newer therapies that block blood vessel growth in the eye. The study found newer therapies could perform just as well, if not slightly better, compared to panretinal photocoagulation without being as destructive to the surrounding eye tissue.[1027] The long-term comparison of these two treatment approaches is ongoing.

The NEI SBIR program funds promising projects at small businesses with the goal of developing and commercializing products for diagnosis, treatment, or rehabilitation of visual impairments. One recent success story led to the development of a semiautomated telemedicine system screen for DR. DR, a leading cause of blindness, is caused by abnormal changes in blood vessels in the retina. Although DR is

[1021] https://ncats.nih.gov/pubs/features/ucla-diabetic-screening.
[1022] https://www.nih.gov/news-events/nih-research-matters/individualized-exam-schedule-diabetic-eye-disease.
[1023] DCCT/EDIC Research Group. *N Engl J Med* 2017;376(16):1507-16. PMID: 28423305.
[1024] https://grade.bsc.gwu.edu/web/grade/home.
[1025] https://clinicaltrials.gov/ct2/show/NCT01942694.
[1026] Park SS. *Invest Ophthalmol Vis Sci* 2016;57(5):ORSFj1-10. PMID: 27116667.
[1027] Sun JK, et al. *Ophthalmology* 2019;126(1):87-95. PMID: 30096354.

treatable if detected early, a significant proportion of diabetic patients do not receive an annual eye exam. Current screening for DR requires manual grading of retinal images by trained specialists, a system that would be overwhelmed by any large-scale community-based screening effort. The telemedicine system can easily and affordably evaluate high volumes of retinal images, taken from geographically remote or underserved communities. The computer-based artificial intelligence system screens for abnormalities, referring patients to the eye doctor as needed. More recently, the classification program has been expanded to screen for other eye diseases, such as glaucoma and macular degeneration. The SBIR program has supported this project from early conceptual phases through clinical development and regulatory assistance. Other SBIR projects are developing and deploying telemedicine tools for screening and diagnosis of eye disease.

More than 100,000 pregnant women with overt type 2 diabetes give birth in the U.S. each year. Strict control of maternal blood sugar is key to optimizing infant outcomes. The Medical Optimization and Management of Pregnancies with Overt Type 2 Diabetes study, supported by NICHD,[1028] is a randomized trial of adding metformin to insulin treatment of overt type 2 diabetes in pregnant women, compared to insulin therapy alone. Metformin is often favored over insulin because it results in less weight gain and fewer hypoglycemic episodes, and it is oral rather than injectable. It also counteracts insulin resistance, which often becomes a problem in type 2 diabetes.

Previous findings show that pregnant women with obstructive sleep apnea (OSA) have an increased risk of diabetes and hypertensive disorders during pregnancy. Through participating sites in the NICHD Maternal and Fetal Medicine Units Network, NICHD and NHLBI support a Phase III randomized clinical trial of treating OSA with continuous positive airway pressure machines that maintain continuous pressure in the airways.[1029] The study will examine rates of GDM and pregnancy-related hypertensive disorders in 2,700 nulliparous pregnant women who have never given birth.

The NIDDK-supported Diabetes Prevention Program Outcomes Study (DPPOS) is following participants in the landmark Diabetes Prevention Program (DPP) to determine long-term outcomes and efficacy of DPP interventions.[1030] DPPOS has found not only that the lifestyle intervention (LI) continues to be effective for at least 15 years but also that LI health benefits are so significant that despite its cost (as originally designed), it reduces need for other health care to the point that its net cost at 10 years is very low. Metformin confers much less benefit than LI, but is so inexpensive that it actually saves a modest amount of money. DPPOS has also made numerous other important findings, including the pharmacogenomic characterization of a gene influencing the transport and effectiveness of metformin, currently the most important medicine in treatment of type 2 diabetes; DPPOS is also examining intervention effects on other outcomes, including diabetes complications and comorbid conditions, such as depression. The third phase of DPPOS, started in 2016, is investigating whether starting metformin during prediabetes leads to lower

[1028] https://projectreporter.nih.gov/project_info_description.cfm?aid=9590212&icde=42209518.
[1029] https://clinicaltrials.gov/ct2/show/NCT03487185.
[1030] https://clinicaltrials.gov/ct2/show/NCT00038727.

rates of CVD and cancer; 67 percent of participants in DPPOS are female, and sex differences in outcome rates will be examined.

Restoring Insulin Secretion (RISE) is an NIDDK-supported consortium that is testing approaches to treatment of people with recent-onset type 2 diabetes or with prediabetes, to determine whether early, aggressive treatment can reduce disease progression.[1031] Two current studies are in adults: one testing medication regimens, and another testing bariatric surgical approaches. Another study tested medicinal approaches in individuals who were 10–19 years of age when they joined the study. The recently published results of this pediatric effort found that neither insulin nor metformin, the two medications approved for treating type 2 diabetes in children, could prevent or delay rapid progression of the glucose imbalance;[1032] the study also found that young people with type 2 diabetes produce much more of their own insulin but have significantly more insulin resistance than people who develop type 2 diabetes later in life.[1033,1034]

Type 1 Diabetes TrialNet is an NIDDK-led international clinical trials network that screens up to 15,000 individuals annually and conducts trials of agents to prevent clinical diagnosis of type 1 diabetes in people with early-stage disease and to slow disease progression in the newly diagnosed.[1035] TrialNet has launched clinical trials of promising prevention strategies, three of which (abatacept, teplizumab, and hydroxychloroquine) are currently ongoing. TrialNet's Oral Insulin Prevention study found that a daily oral dose of insulin did not delay type 1 diabetes onset in at-risk relatives of people with the disease.[1036] TrialNet researchers also found that treatment with a single course of anti-thymocyte globulin preserved insulin production in people with newly diagnosed type 1 diabetes for at least 1 year, but that addition of granulocyte-colony stimulating factor did not enhance benefit.[1037]

NIDDK published a report highlighting the exciting achievements made in type 1 diabetes research and improvements in health and lives of people with the disease.[1038] Research leading to these advances was supported by the Special Statutory Funding Program for Type 1 Diabetes Research, a special appropriation dedicated to supporting research on the prevention, treatment, and cure of type 1 diabetes and its complications. The report describes pioneering discoveries, both emerging and expected to emerge from this long-term, unique funding program.

The NIDDK-led Preventing Early Renal Function Loss in Diabetes clinical trial completed the study and is analyzing data to determine whether the drug allopurinol (currently used for the treatment of gout) could

[1031] https://rise.bsc.gwu.edu/web/rise.
[1032] RISE Consortium. *Diabetes Care* 2018;41(8):1717-25. PMID: 29941500.
[1033] RISE Consortium. *Diabetes Care* 2018;41(8):1696-1706. PMID: 29941497.
[1034] RISE Consortium. *Diabetes Care* 2018;41(8):1707-16. PMID: 29941498.
[1035] https://www.trialnet.org/.
[1036] Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group. *JAMA*. 2017;318(19):1891-1902. PMID: 29164254.
[1037] Haller MJ, et al. *Diabetes Care* 2018;41(9):1917-25. PMID: 30012675.
[1038] https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/special-statutory-funding-program-for-type-1-diabetes-research-progress-report.

preserve kidney function in people with type 1 diabetes who are at high risk of kidney disease.[1039] The trial has the potential to identify an inexpensive approach to preserving kidney function in people with type 1 diabetes.[1040]

The Clinical Islet Transplantation Consortium, co-led by NIDDK and NIAID, completed a Phase III clinical trial that evaluated the risk and benefits of islet transplantation in people with type 1 diabetes with impaired awareness of hypoglycemia and high risk of severe hypoglycemic events.[1041] The trial found that during the first year after transplantation, 88 percent of participants were free of severe hypoglycemic events, had near-normal control of BG events, and had restored hypoglycemic awareness.[1042] After 2 years, 71 percent of participants continued to meet these criteria for a transplant success.

NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow-up, Epidemiology of Diabetes Interventions and Complications Study (EDIC), have demonstrated that a short period of intensive glucose control early in life prevents or delays for decades complications of the heart, kidney, nerves, and eyes in patients with type 1 diabetes.[1043] DCCT/EDIC researchers recently reported that patients who practiced intensive BG management during DCCT (compared with patients who did not) had a 30 percent reduced incidence of CVD and 32 percent fewer major cardiovascular events after 30 years of follow-up.[1044] DCCT participants who had practiced intensive BG management also tended to live longer than participants who did not.[1045] EDIC researchers also demonstrated that adjusting the frequency of eye screenings for people with type 1 diabetes based on their diabetes management and risk of eye problems could result in both fewer eye exams and better eye health.

NEI's NEHEP partnered with ADA to conduct NEHEP's first Facebook Live event, *For your eyes only: Let's talk diabetes and eye health*,[1046] to educate audiences about vision complications as a result of diabetic eye diseases. The video received 11,875 total views and won a first-place Blue Pencil and Gold Screen Award in social media from the National Association of Government Communicators.

NIDDK-supported research contributed to the development of the first commercially available hybrid artificial pancreas device approved by FDA in 2016 and has contributed to the development or testing of several new FDA-approved continuous glucose monitors. Building on this success, NIDDK is supporting advanced clinical trials that could pave the way toward FDA approval of new artificial pancreas devices, as well as supporting research to develop next-generation glucose management technologies. Research continues to demonstrate benefits of artificial pancreas technologies, such as a study showing that compared to usual care, artificial pancreas use in adolescents with type 1 diabetes improved their BG

[1039] http://www.perl-study.org/.
[1040] This study was unlikely to be supported by the private sector because it is testing a generic drug.
[1041] https://www.citisletstudy.org.
[1042] Hering BJ, et al. *Diabetes Care* 2016;39(7):1230-40. PMID: 27208344.
[1043] https://portal.bsc.gwu.edu/web/edic/home.
[1044] Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. *Diabetes Care* 2016;39(5):686-93. PMID: 26861924.
[1045] Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. *Diabetes Care* 2016;39(8):1378-83. PMID: 27411699.
[1046] https://www.facebook.com/AmericanDiabetesAssociation/videos/10153985167514033/.

management and reduced hypoglycemia during extended vigorous outdoor exercise at ski camp, a finding that helps advance artificial pancreas use in more physically demanding and real-world conditions.[1047]

Digestive Diseases

Digestive diseases span a wide spectrum of illnesses and disorders that affect the gastrointestinal (GI) tract, liver, gallbladder, and pancreas, and many forms are chronic. Some digestive diseases, such as gastroesophageal reflux disease, are common; others, such as genetic forms of liver disease, are quite rare. Collectively, digestive diseases exact a significant toll on public health in terms of quality of life, years of life lost due to premature death, and costs associated with hospitalizations and pharmaceutical and surgical interventions. For example, more than 30 million visits to a doctor or emergency room in 2016 in the U.S. were due to diseases within the digestive system.[1048] NIH's research spans the breadth of the many different digestive diseases affecting Americans, from investigating the diseases' biological and basic underpinnings to improving how they are treated and prevented.

Understanding Prevalence, Risk Factors, and Underlying Biology

A study used an online survey of parents to assess the prevalence of pediatric functional GI disorders in a representative community sample using the newly developed Rome IV criteria. The study found that 24.7 percent of infants and toddlers and 25 percent of children and adolescents ages 4–18 years met the symptom-based criteria for having a GI disorder.[1049] Decreased quality of life was associated with meeting the criteria for a functional GI disorder.

An imbalance in intestinal microbes can correlate with GI symptoms. Researchers analyzed blood and stool samples from four groups of children: (1) children with ASD and GI symptoms; (2) children with ASD, but without GI symptoms; (3) children with GI symptoms, but not ASD; and (4) children with neither ASD nor GI symptoms. The scientists found that children with ASD who also experience GI symptoms have an imbalance in their immune system responses.[1050] The researchers also suggested that imbalance in the intestinal microorganisms that help with digestion may play a role in these problems.

In a study to determine whether celiac disease is more common in some geographic regions than others, which could help pinpoint factors involved in the onset of the disease, NIDDK-supported scientists combed through U.S. health data and found that people living north of latitude 40° North (approximately the northern border of Kansas) were more than five times as likely to have celiac disease as those living south of 35° North (approximately the southern border of Tennessee).[1051] The reasons for a higher frequency of celiac disease in northern states are not clear, but the trend appears to be independent of race, ethnicity,

[1047] Breton MD, et al. *Diabetes Care* 2017;40(12):1644-50. PMID: 28855239.
[1048] https://www.cdc.gov/nchs/fastats/digestive-diseases.htm.
[1049] Robin SG, et al. *J Pediatr* 2018;195:134-9. PMID: 29398057.
[1050] Rose DR, et al. *Brain Behav Immun* 2018;70:354-68. PMID: 29571898.
[1051] Unalp-Arida A, et al. *Gastroenterology* 2017;152(8):1922-32.e2. PMID: 28238771.

socioeconomic status, and body mass index, suggesting that genetic or environmental factors could be involved.

Stress is known to perturb the microbiome and exacerbate IBS-associated symptoms. Indeed, an analysis of the microbiome in a rat model of stress-induced IBS revealed structural and functional changes, including changes in sulfur metabolism, that could serve as targets in restoring the healthy microbiome in individuals with IBS.[1052]

The NIDDK Inflammatory Bowel Disease (IBD) Genetics Consortium is a major driver of the Institute's research program on the role of genetic factors in the development of Crohn's disease and ulcerative colitis. The consortium is part of an international IBD genetics consortium that has aided in increasing the power of analyses to enable discovery of additional risk variants for IBD.[1053] Recent findings from studies involving the NIDDK's IBD Genetics Consortium uncovered two genetic variants that increase the risk for IBD and also provide clues to their functional impacts, including interactions with the immune system and gut microbes.[1054,1055] Another study found that there are actually two genetically distinct types of Crohn's disease, which could help guide targeted treatments in the future.[1056]

NIDDK worked closely with other NIH ICs and the NIH Common Fund in supporting research through the Human Microbiome Project, which contributed to advancing understanding of IBD and the role of gut microbial factors. The Inflammatory Bowel Disease Multi'omics Database, part of the second phase of the Human Microbiome Project launched in 2014, was a multi-institutional effort to understand how the human gut microbiome changes over time in adults and children with IBD.[1057] The overall goal of this study was to provide translationally actionable targets for IBD therapy or diagnosis. The researchers found that the microbiomes of people with IBD were more volatile and fluctuated to a greater extent than those of healthy people, providing still more evidence that changes in the microbiome are closely linked to the disease.[1058]

Additionally, NIDDK-supported studies that delve into the genetics of IBD have pointed to abnormal interactions between the gut and the bacteria inhabiting it, implicating genetic defects in autophagy, which is a process that cells can use to break down microbial material.[1059,1060] Another NIDDK-supported study found that alterations in gut microbial communities caused by antibiotic treatments can pass from pregnant mice to their offspring and increase the offspring's risk for intestinal inflammation similar to

[1052] Fourie NH, et al. *Gut Microbes* 2017;8(1):33-45. PMID: 28059627.
[1053] http://ibdgc.uchicago.edu/.
[1054] Chuang LS, et al. *Gastroenterology* 2016;151(4):710-23.e2. PMID: 27377463.
[1055] Li D, et al. *Gastroenterology* 2016;151(4):724-32. PMID: 27492617.
[1056] Cleynen I, et al. *Lancet* 2016;387(10014):156-67. PMID: 26490195.
[1057] https://ibdmdb.org/.
[1058] Halfvarson J, et al. *Nat Microbio.* 2017;2:17004. PMID: 28191884.
[1059] Chu H, et al. *Science* 2016;352(6289):1116-20. PMID: 27230380.
[1060] Lassen KG, et al. *Immunity* 2016;44(6):1392-405. PMID: 27287411.

human IBD.[1061] Researchers supported by NIDDK also found that an enzyme produced by certain bacteria could disrupt the gut microbiome, potentially playing a significant role in the development of IBD.[1062]

An NIDDK-supported study found that infection with a reovirus, a common type of virus to which people are typically exposed throughout their lives, may trigger celiac disease in individuals who are genetically susceptible to developing the disorder.[1063] The researchers found that a reovirus infection disrupted the immune system in mice carrying a human genetic variant that confers susceptibility to celiac disease, preventing the mice from developing tolerance to ingested gluten. The scientists also found that people with celiac disease had higher levels of antibodies to reoviruses than people without the disease, providing evidence linking celiac disease to immune responses from reovirus infections.

Other ongoing NIDDK-supported studies focused on the role of the gut microbiome in childhood undernutrition. One study in which researchers collected fecal samples from children living in Bangladesh showed that pathogenic microbes from a malnourished child caused weight loss when transplanted into mice without other microbes present, whereas simultaneously transplanting the pathogenic microbe together with harmless microbes from a normal-weight child cancelled out the pathogenic strain's ability to cause weight loss in mice.[1064] Two other studies conducted in Malawi showed how an immature community of microorganisms housed in the guts of children with undernutrition contributed to impaired growth and how unique nutrients found in milk can interact with these microbes to foster growth.[1065,1066] Findings from these studies may be used to better understand how microbes influence childhood undernutrition and to design more effective therapeutic and preventive strategies.

Hirschsprung's disease, caused by missing nerve cells in the muscles of part or all of the large intestine, results in difficulty in having bowel movements. NICHD is supporting a genetic analysis of Hirschsprung's disease to describe the genes, sequence variants, and biochemical pathways that affect the disease.[1067] The researchers are using state-of-the-art technologies to screen the genomes of patients with Hirschsprung's disease, as well as their affected relatives and their parents.

In FY 2017, NIDDK issued a FOA to encourage basic and translational research on improving understanding of the role of lymphatics of the digestive system in health and disease.[1068] The NIDDK also continued to actively fund research in this area that resulted from a FOA issued in 2015 to support research on lymphatic vessel physiology, development, and pathophysiology related to health and disease.[1069]

[1061] Schulfer AF, et al. *Nat Microbiol* 2018;3(2):234-42. PMID: 29180726.
[1062] Ni J, et al. *Sci Transl Med* 2017;9(416). pii: eaah6888. PMID: 29141885.
[1063] Bouziat R, et al. *Science* 2017;356(6333):44-50. PMID: 28386004.
[1064] Wagner VE, et al. *Sci Transl Med* 2016;8(366):366ra164. PMID: 27881825.
[1065] Blanton LV, et al. *Science* 2016;351(6275). pii: aad3311. PMID: 26912898.
[1066] Charbonneau MR, et al. *Cell* 2016;164(5):859-71. PMID: 26898329.
[1067] https://projectreporter.nih.gov/project_info_description.cfm?aid=9691015&icde=43381630.
[1068] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-016.html.
[1069] https://grants.nih.gov/grants/guide/pa-files/PAR-15-306.html.

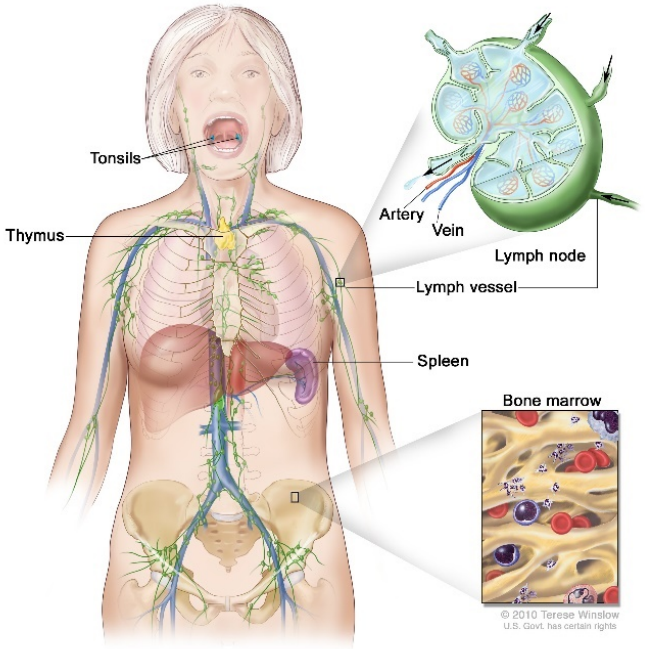

Figure 64. Diagram of the lymph system. Credit: Teresa Winslow.

NIDDK, in partnership with NCI, continued support for the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer to conduct studies of people with chronic pancreatitis to improve understanding of disease processes and related outcomes, such as diabetes and pancreatic cancer development.[1070] As part of the consortium, NCI and NIDDK funded a grant throughout FY 2016–2018 to support a pediatric pancreatitis consortium within this larger network called INSPPIRE (InterNational Study group of Pediatric Pancreatitis: In search for a cuRE). In FY 2016, this international group of researchers published a study identifying risk factors, including genetic variants, for pancreatitis development in children.[1071]

In FY 2016–2018, NIDDK continued support for the Childhood Liver Disease Research Network (ChiLDReN),[1072] which sponsors clinical and translational research to improve understanding of rare pediatric liver diseases, including biliary atresia, Alagille syndrome, alpha-1-antitrypsin deficiency, Progressive Familial Intrahepatic Cholestasis syndromes; bile acid synthesis defects; mitochondrial hepatopathies; idiopathic neonatal hepatitis; and cystic fibrosis–associated liver disease. In FY 2018, NIDDK released a FOA to continue this network, supporting studies for up to 5 years.[1073,1074] By analyzing blood samples from infants enrolled in the ChiLDReN study, researchers found that levels of an enzyme called matrix metalloproteinase-7 (MMP-7) were higher in infants with biliary atresia, a potentially fatal

[1070] https://cpdpc.mdanderson.org/index.html.
[1071] Kumar S, et al. *JAMA Pediatr* 2016;170(6):562-9. PMID: 27064572.
[1072] https://childrennetwork.org/.
[1073] https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-18-501.html.
[1074] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-502.html.

form of pediatric liver disease.[1075] MMP-7 inhibitors protected against bile duct destruction in a mouse model of the disease. These findings suggest that MMP-7 is not only a promising candidate as a much-needed biomarker for improving early diagnosis of biliary atresia, but also likely plays a role in disease development and may be a therapeutic target. Also, in FY 2018, network researchers published results of a GWAS identifying a potential susceptibility gene for biliary atresia that could yield insights into understanding disease mechanisms.[1076]

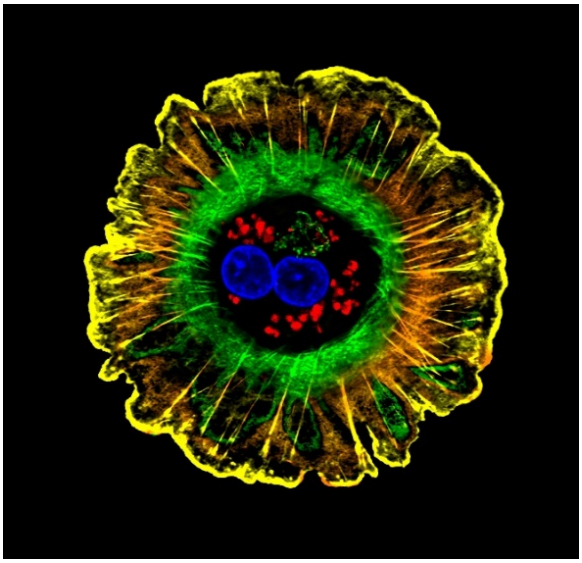

Figure 65. Human liver cell in culture. Credit: Donna Beer Stolz, University of Pittsburgh.

NIDDK, together with NIAID, continued support for the Intestinal Stem Cell Consortium,[1077] established in 2009 to stimulate basic research through developing new technologies to isolate, characterize, cultivate, and manipulate intestinal stem cells. In FY 2018, a new FOA was released to continue the consortium's work advancing understanding of intestinal epithelial stem cell biology, with the ultimate goal of developing novel therapies targeting these stem cells and their supportive niche to regenerate and rebuild the human intestine.[1078]

NIDDK-supported researchers uncovered a key role for a unique cell type called a telocyte in supporting proliferation and maturation of the nearby intestinal stem cells that perpetually replenish the inner lining of the gut. The telocytes accomplish this feat by regulating important growth signals sent to the stem cells.[1079] This research illuminates the importance of telocytes in supporting the source of the intestinal lining's regenerative capacity. Future studies can build on this work to explore the nature of these telocytes and their role in the intestine.

[1075] Lertudomphonwanit C, et al. *Sci Transl Med* 2017;9(417). PMID: 29167395.
[1076] Chen Y, et al. *PLoS Genet* 2018;14(8):e1007532. PMID: 30102696.
[1077] https://iscconsortium.org/.
[1078] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-507.html.
[1079] Shoshkes-Carmel M, et al. *Nature* 2018;557(7704):242-6. PMID: 29720649.

Improving Treatment and Prevention

On June 23–24, 2016, NIDDK sponsored a workshop on the future direction of research on the pathophysiology, diagnosis, and treatment of functional bowel disorders, including IBS and fecal incontinence.[1080] Among the topics discussed were recent advances in the understanding of genetic and environmental factors, including the microbiome and psychosocial factors, that contribute to functional bowel disorders. New ways to diagnose functional bowel disorders were also discussed, including efforts to identify and detect associated physiological changes. The knowledge shared at this workshop was published in a major scientific journal and helped steer research toward providing new pathways for diagnosis and treatment for these disorders.[1081]

NIH Director Dr. Francis Collins established the NIH Nutrition Research Task Force in October 2016 to coordinate and accelerate progress in nutrition research across the NIH.[1082] The Task Force is chaired by Dr. Griffin Rodgers, NIDDK Director, and co-chaired by Dr. Gary Gibbons, NHLBI Director; Dr. Norman Sharpless, NCI Director; and Dr. Diana Bianchi, NICHD Director. Additional leadership is provided by NIDDK's Office of Nutrition Research. Since its establishment, the Task Force has guided the development of the first NIH-wide 10-year strategic plan for nutrition research, which emphasizes crosscutting innovative opportunities to advance nutrition research across a wide range of areas, including basic, translational, and clinical research, as well as research training activities.

An NINR intramural research scientist, in collaboration with an industry scientist, co-invented a new patent-pending methodology to test stool rapidly, at the point of need, for infectious pathogens. This first-of-a-kind test is done at the point of care and without a laboratory, allowing clinicians to treat patients immediately, because the test results are provided within minutes as opposed to days.[1083] In addition to providing fast results, the paper-based test has the potential to improve outcomes, especially in resource-limited settings in the developing world, where 500,000 children a year die from diarrheal diseases.

In FY 2016–2018, NIDDK, in conjunction with the National Library of Medicine, supported the *LiverTox* website.[1084] This website features sample cases of drug-induced liver injury, as well as a database with summaries of liver injury reports for a given drug or herbal/dietary supplement. The website serves as a public resource to aid health care providers in diagnosing—and investigators in studying—liver injury due to drugs and herbs/supplements.

On July 25, 2018, NIDDK, with support from the National Pancreas Foundation, sponsored a workshop to identify research gaps and opportunities in the development of new drugs and clinical testing approaches to managing acute and chronic forms of pancreatitis.[1085] The workshop brought together presenters and participants from NIH, FDA, researchers from the U.S. and other countries, health care organizations,

[1080] https://www.niddk.nih.gov/news/meetings-workshops/2016/fbdworkshop2016.
[1081] Chang L, et al. *Gastroenterology* 2018;154(3):723-35. PMID: 29288656.
[1082] https://www.niddk.nih.gov/about-niddk/advisory-coordinating-committees/nih-nutrition-research-task-force.
[1083] https://www.ninr.nih.gov/newsandinformation/newsandnotes/henderson-shark-tank.
[1084] https://www.ncbi.nlm.nih.gov/books/NBK547852/.
[1085] https://www.niddk.nih.gov/news/meetings-workshops/2018/accelerating-drug-delivery-pipeline-pancreatitis.

pharmaceutical industry representatives, and patient advocacy groups with a goal of sparking research to enhance development of new treatments and testing methods for pancreatitis. Multiple papers in the scientific literature have been published summarizing the workshop proceedings, and recommendations will inform future efforts of NIDDK, along with other research partners, to advance research in this area.[1086–1089]

On September 26–27, 2018, NIDDK hosted a workshop to explore approaches to research on dietary biomarkers.[1090] Workshop participants discussed challenges to biomarker discovery, new tools for biomarker identification and validation, platforms for sharing data, and new opportunities to use biomarkers in nutrition research. Recommendations from the workshop will be made available through publication in a scientific journal, with the goal of improving nutrition research by highlighting new ways to examine the link between dietary components and health outcomes.

NIDDK continued support of its current research efforts in digestive diseases and also pursued new directions. For example, NIDDK issued two initiatives in FY 2018 to renew support for the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network[1091] supporting projects for up to 5 more years.[1092,1093] The network's future goals include continuing to support the clinical sites of the research network as they complete active clinical treatment trials and continuing to longitudinally gather biospecimens and data from children and adults with nonalcoholic fatty liver disease (NAFLD).

The NIDDK's Drug-Induced Liver Injury Network collects and analyzes cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines, such as herbal products and supplements.[1094] In FY 2017, network researchers published three studies providing new insights into outcomes from this potentially severe form of liver injury, including the rate of fatal outcomes, frequency of bile duct damage and loss, and racial and ethnic disparities in disease severity. NIDDK has continued to support this network through a FOA released in 2017 to extend studies for up to 5 years starting in 2018.[1095,1096]

The NIDDK-supported Methotrexate Response in Treatment of Ulcerative Colitis (MERIT-UC) study investigated the safety and therapeutic value of methotrexate, an inexpensive yet potentially toxic drug that is used in adult ulcerative colitis patients in whom established therapies have failed. Results from this study showed that methotrexate did not improve ulcerative colitis symptoms compared to a placebo, suggesting that this drug, which could lead to chronic liver disease and liver fibrosis, is not beneficial for

[1086] Uc A, et al. *Pancreas* 2018;47(10):1180-4. PMID: 30325855.
[1087] Abu-El-Haija M, et al. *Pancreas* 2018;47(10):1185-92. PMID: 30325856.
[1088] Lowe ME, et al. *Pancreas* 2018;47(10):1193-9. PMID: 30325857.
[1089] Forsmark CE, et al. *Pancreas* 2018;47(10):1200-7. PMID: 30325858.
[1090] https://www.niddk.nih.gov/news/meetings-workshops/2018/workshop-biomarkers-dietary-intake-exposure.
[1091] https://jhuccs1.us/nash/.
[1092] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-505.html.
[1093] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-506.html.
[1094] https://dilin.org/.
[1095] https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-17-509.html.
[1096] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-510.html.

colitis patients.[1097] The Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study, also supported by NIDDK, has been evaluating whether a combination of clinical, genetic, and immunologic tests can be used to predict response to standard medical therapy for children newly diagnosed with ulcerative colitis. One finding from the PROTECT study was that ulcerative colitis correlates with vitamin D deficiency in pediatric patients, raising the possibility that vitamin D deficiency might contribute to the progression of the disease.[1098]

The NIDDK-sponsored Fecal Incontinence Treatment Study, launched in 2018, is comparing three previously validated treatments for fecal incontinence: biofeedback (mental and physical training with insertable devices to increase control of anal muscles and response to feelings of pressure), sacral nerve stimulation (electric stimulation of pelvic nerves to improve bowel function, which requires surgery to implant a wire in the lower back), and injection of an inert bulking agent (dextranomer) under the lining of the anal canal to increase barrier function.[1099] The study participants will be followed for 2 years, and the treatments will be compared on the basis of efficacy, safety, and cost.

NIDDK supported studies published in FY 2016 that researchers performed in cell and animal models on a plant toxin, called biliatresone, which is capable of causing bile duct injury in these models similar to biliary atresia, a serious liver disease of early infancy.[1100,1101] These studies provided insights into the molecular processes that may contribute to this pediatric liver disease. These findings may aid in the development of new treatment or prevention strategies.

During FY 2016–2018, NIDDK continued to support the work of the adult Acute Liver Failure Study Group by enrolling patients with acute liver failure (ALF) into a clinical database, increasing the numbers of well-characterized biospecimens stored in a central repository, and continuing innovative clinical investigation into the causes and means of treatment of ALF and the complications that emanate from ALF.[1102] In FY 2016, the group published results from a 16-year study showing that outcomes and survival have improved for people experiencing ALF, including both those who did and those who did not receive a liver transplant.[1103]

With gastroenteritis, one cause of stomach flu, the stomach and intestines become irritated and inflamed, typically due to viral or bacterial infections. Probiotics are often recommended for children with acute gastroenteritis. However, in a large study at 10 children's emergency rooms across the U.S., researchers found that a probiotic treatment did not show any benefit for young children brought to the hospital with acute gastroenteritis.[1104] For every outcome, in every subgroup of patients, the probiotic made no difference.

[1097] Herfarth H, et al. *Gastroenterology* 2018;155(4):1098-108.e9. PMID: 29964043.
[1098] Sauer CG, et al. *Inflamm Bowel Dis* 2018;24(3):641-50. PMID: 29462384.
[1099] https://projectreporter.nih.gov/project_info_description.cfm?aid=9427537.
[1100] Zhao X, et al. *Hepatology* 2016;64(3):894-907. PMID: 27102575.
[1101] Waisbourd-Zinman O, et al. Hepatology. 2016;64(3):880-93. PMID: 27081925.
[1102] https://www.utsouthwestern.edu/labs/acute-liver/overview/.
[1103] Reuben A, et al. *Ann Intern Med* 2016;164(11):724-32. PMID: 27043883.
[1104] Schnadower D, et al. *N Engl J Med* 2018;379(21):2002-14. PMID: 30462938.

Children with obesity are more likely than non-obese peers to experience gastroesophageal reflux disease (GERD), but NICHD-supported clinical research indicates that that simply increasing the dosing of a proton-pump inhibitor drug (pantoprazole) to treat pediatric GERD, on the basis of young patients' excess weight, is problematic. A pharmacokinetic study supported by NICHD found higher exposures and slower clearance of the drug in children with obesity, compared with historical controls, which indicated reduction of, not increase of, pediatric proton-pump inhibitor dosing for GERD.[1105] They reported also that observed pharmacokinetic differences between children and adolescents in the trial may not be simply a matter of body size, but may also reflect the effects of obesity on certain drug-metabolizing enzymes.

Eye Disease and Disorders of Vision

Diseases and disorders of the eye affect millions of Americans and create a significant burden for those afflicted, as well as for society at large. For example, more than 3.3 million Americans over the age of 40 are either legally blind or have low vision.[1106] Age-related macular degeneration (AMD), which results in damage to sharp and central vision and is a leading cause of blindness, affects 1.8 million Americans, with another 7.3 million at risk for developing it.[1107] Cataracts, another common and burdensome disorder, result in clouded vision and are the leading cause of blindness across the world. In the U.S., more than 20 million Americans over the age of 40 are estimated to have cataracts in one or both eyes. In fact, vision loss ranks among the top ten causes of disability in the U.S., and as the population of older people continues to increase, the number of people experiencing vision loss will continue to increase.[1108] These and many other common ocular diseases and disorders, such as glaucoma and diabetic retinopathy, are part of NIH's broad ocular research portfolio, led by NEI. Additional updates related to neural degeneration in eye diseases are presented in the Neuroscience section of this chapter.

Figure 66. Dr. Emily Chew of the NEI examines a patient's eyes. Credit: NEI.

[1105] Shakhnovich V, et al. *J Pediatr* 2018;193:102-8.e1. PMID: 29389444.
[1106] https://www.cdc.gov/visionhealth/basics/ced/.
[1107] https://www.cdc.gov/visionhealth/basics/ced/.
[1108] https://www.cdc.gov/visionhealth/basic_information/vision_loss.htm.

Understanding Prevalence, Risk Factors, and Underlying Biology

Subterranean animals, such as blind cavefish, provide a unique opportunity to study how animals thrive in extreme environments, some of which can mimic human conditions. According to a study conducted by intramural researchers at NICHD, the loss of eye tissue in blind cavefish, which occurs within a few days of their development, happens through a complex process known as epigenetic signaling.[1109] Epigenetic regulation is a process in which genes are turned off or on, typically in a reversible or temporary manner; this mechanism differs from genetic mutations, which are permanent changes in the DNA code. Many of the cavefish genes identified in this study are also linked to eye disorders in humans. This linkage suggests that the genes are conserved across evolution and may be similarly regulated in people.

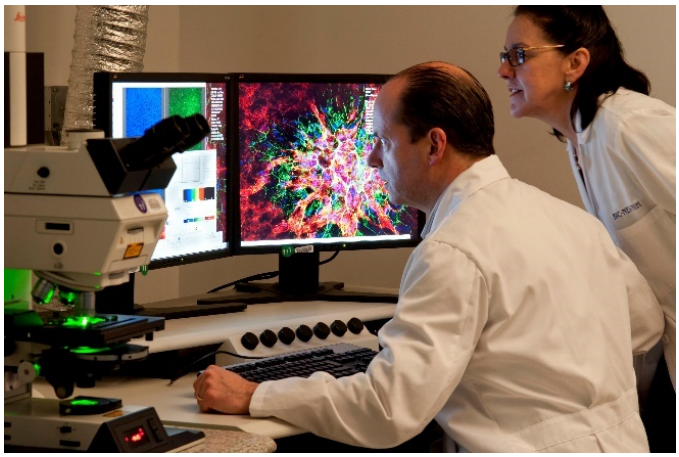

Figure 67. Two NEI scientists observe ocular tissue samples under a laser scanning microscope. Credit: NEI.

NLM is collaborating with the NEI Division of Epidemiology and Clinical Applications in developing machine learning (deep learning, artificial intelligence) and image analysis–based algorithms for detecting and quantifying age-related eye diseases, including macular degeneration and diabetic retinopathy.

AMD is the leading cause of irreversible blindness in the developed world, and its cause remains elusive. Researchers have long suspected that the immune system plays a role in disease pathogenesis, but the key instigative events and culprits remain unknown. NEI-funded researchers discovered a protein known as cGAS that may be responsible for some of the initial events that trigger the immune system's overactivity in geographic atrophy, an advanced form of AMD.[1110] Normally involved with initiating immune responses against viruses and bacteria, cGAS activity has also been linked to other diseases with known or suspected immune system contributors, such as diabetes, lupus, and obesity. The research community is currently working to identify how to target this factor for future therapeutic development.

Glaucoma, a disease characterized by high intraocular pressure (IOP) and progressive peripheral vision loss, is one of the most common causes of irreversible vision loss worldwide and has a complex underlying biology. Although family history of glaucoma has been known as one of the largest risk factors for decades,

[1109] Gore AV, et al. *Nat Ecol Evol* 2018;2(7):1155-60. PMID: 29807993.
[1110] Kerur N, et al. *Nat Med* 2018;24(1):50-61. PMID: 29176737.

the complicated interplay of many genes and environmental influences has thwarted researchers' efforts at pinpointing disease-causing genes. The NEI Glaucoma Human genetics collaBORation (NEIGHBOR) consortium connects clinical researchers to the largest network of the most thoroughly characterized population of glaucoma patients in the world. NEI-funded researchers applied new genomics tools to study almost 140,000 glaucoma patients and healthy volunteers in the U.S. and Europe and identified more than 130 genetic variants associated with increased IOP.[1111] Detailed analysis of these data allowed the team to predict a person's risk of developing glaucoma with 75 percent accuracy, providing a significant leap forward for researchers looking for ways to prevent the disease or slow progression.

Retinal ganglion cells (RGCs), a cell type in the retina responsible for carrying vision information through the optic nerve to the brain, succumb to high pressure in the eye. As RGCs die, the signals cannot get to the brain, corresponding to vision loss in glaucoma patients. NEI-funded researchers found that nicotinamide adenine dinucleotide (NAD), an essential molecule for numerous biological processes, decreases in older patients and in animal models of glaucoma.[1112] Cells make NAD from vitamin B3 with a protein called Nmnat1. Vitamin B3 administration allowed RGCs to withstand high pressure, as did gene therapy of *Nmnat1*. The group that conducted the research is currently identifying clinical partnerships to begin testing vitamin B3 administration in glaucoma patients in a clinical trial.

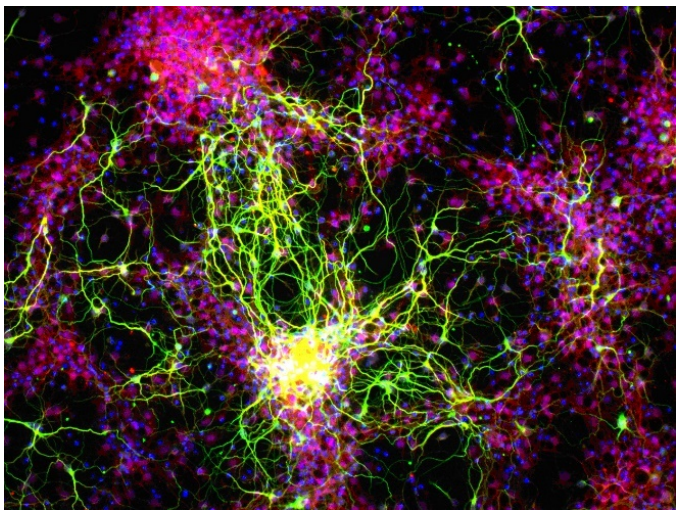

Figure 68. Retinol ganglion cells. Credit: NEI, NIH (Courtesy of Thomas V. Johnson, Naoki Nakaya, and Stanislav Tomarev of the NEI Laboratory of Retinal Cell and Molecular Biology, Molecular Mechanisms of Glaucoma Section).

Fuchs endothelial corneal dystrophy is a degenerative disease affecting 4 percent of patients 40 years of age or older that can result in vision-threatening damage to the cornea, the transparent tissue in the front of the eye. Often, the damage to the cornea is so severe it requires a cornea transplant; most corneal transplants are needed because of Fuchs endothelial corneal dystrophy. Unfortunately, the cause of the disease is still largely unclear. NEI-funded researchers working with an international team of geneticists identified three novel genes associated with the disease: *KANK4, LAMC1*, and *ATP1B1*.[1113] This research

[1111] Khawaja AP, et al. *Nat Genet* 2018;50(6):778-82. PMID: 29785010.
[1112] Williams PA, et al. *Science*. 2017;355(6326):756-60. PMID: 28209901.
[1113] Afshari NA, et al. *Nat Commun* 2017;8:14898. PMID: 28358029.

also supported previous studies that identified the gene *TCF4* as linked to the disease. These findings will help guide future research efforts aimed at uncovering the basic biology underlying disease pathogenesis.

Retinitis pigmentosa is a group of inherited retinal degenerative diseases characterized by reduced vision, especially in dim light, and constricted field of view (*tunnel vision*). NEI intramural researchers have shown that one form of retinitis pigmentosa is caused by mutations in the *CLCC1* gene, which codes for a protein that controls the flow of chloride in and out of the cell.[1114] These observations help our general understanding of this group of retinal degenerations and suggest potential therapeutic strategies.

Animal models, although invaluable in many basic research projects and much preclinical work, often fail to faithfully recapitulate key features of living tissue in humans. NEI launched the $1.1 million 3-D Retina Organoid Challenge (3D-ROC) competition to catalyze interest and development of three-dimensional retina tissue models generated from human iPSCs for use in basic research, drug screening, and disease modeling.[1115] Initial phases challenged researchers and industry partners to improve upon current methods for generating retina organoids, either by demonstrating significant improvements in similarity to in vivo tissue, by significantly improving upon production scalability, or a combination of the two. The winner of the first phase of the challenge was awarded money to develop a plan to 3-D print tissues for research. More recent phases challenged researchers and industry partners to focus on disease modeling and retina organoid utilization in high-throughput drug screening.

Improving Treatment and Prevention

AMD is the leading cause of irreversible blindness in the developed world, and the incidence of the disease is expected to skyrocket by 2050 as the population ages. Although most patients with AMD will not progress to the advanced forms of the disease, ophthalmologists and basic researchers still have no robust biomarkers capable of accurately predicting advanced disease in patients. NEI launched the AMD Ryan Initiative Study to test whether the presence of reticular pseudodrusen, a specific morphological aberration in the eye readily detectable by current widely available imaging techniques in the clinic, can accurately predict which patients with early-stage disease will progress to advanced disease stages.[1116] Participating study sites in the U.S., United Kingdom, Australia, Germany, and Italy will collect data.

[1114] Li L, et al. *PLoS Genet* 2018;14(8):e1007504. PMID: 30157172.
[1115] https://nei.nih.gov/about/goals-and-accomplishments/nei-research-initiatives/3-d-retina-organoid-challenge-3-d-roc.
[1116] https://clinicaltrials.gov/ct2/show/NCT03092492.

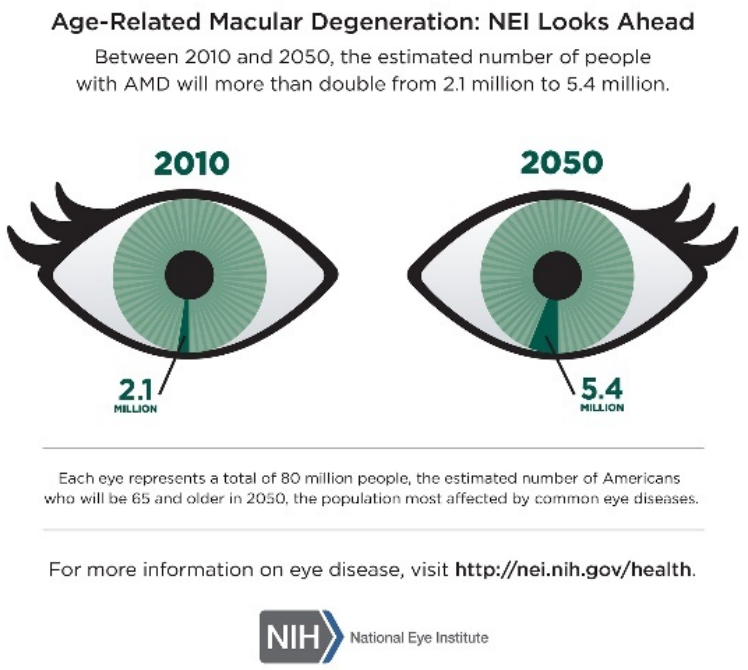

Figure 69. "Age-Related Macular Degeneration: NEI Looks Ahead": Infographic. Credit: NEI.

Many patients suffering from dry eyes have taken fish oil supplements, despite insufficient evidence of their effectiveness. The Dry Eye Assessment and Measurement Study tested the safety and efficacy of daily high doses of omega-3 fatty acid supplementation (from fish oil) in patients suffering from chronic moderate to severe dry eye disease. After 12 months of daily supplementation, no significant difference in disease improvements was observed between patients taking omega-3 fatty acids and those taking placebo; the supplements failed to yield benefit to patients.[1117] Supplements can be very expensive; thus studies such as this and other NIH clinical trials that are not likely to be conducted in the private sector are important for testing the safety and efficacy for treatments already on the market.

Mesenchymal cells are a type of cell that direct wound healing following injury, and they become active in the eye following cataract surgery. Unfortunately, these mesenchymal cells sometimes turn into myofibroblasts, a cell type responsible for forming scar tissue. Excessive scarring following cataract surgery can complicate the benefits patients gain after having a cataract removed. How beneficial mesenchymal cells can transition to myofibroblasts is not entirely clear. A group of NEI-funded researchers found a factor called vimentin that may be partly responsible for the excessive scarring sometimes seen after cataract surgery.[1118] This work has the potential to help researchers and clinicians determine ways to limit scarring after cataract surgery.

[1117] Dry Eye Assessment and Management Study Research Group, et al. *N Engl J Med* 2018;378(18):1681-90. PMID: 29652551.
[1118] Walker JL, et al. *Mol Biol Cell* 2018;29(13):1555-70. PMID: 29718762.

The NEI Audacious Goals Initiative (AGI) program aims to regenerate neuronal function in the retinae and optic nerves of patients damaged by blinding diseases like glaucoma and AMD.[1119] AGI challenges the research community to collaborate and create innovative approaches to imaging, treatment, and disease modeling in order to overcome barriers and bring regenerative medicine therapies to the clinic. Previous rounds of AGI awardees formed interdisciplinary teams to create novel imaging techniques, form consortiums to share data and methodologies, and identify neuroregenerative factors. AGI now turns its attention to generating new animal and disease models;[1120] five awardees are currently establishing non-mouse animal models to study retinal degeneration and regenerative therapies.[1121]

Kidney Disease

The kidneys—two bean-shaped organs about the size of a fist—filter extra water and wastes out of the blood and make urine. Kidney diseases result in damaged kidneys that cannot filter blood the way they should. Loss of function of these organs can result in life-threatening complications.[1122] More than 1 in 7 U.S. adults suffer from kidney diseases,[1123] including chronic kidney disease (CKD), which affects an estimated 37 million adults.[1124] NIH's research efforts, led by NIDDK, seek to understand how and why kidney diseases develop, prevent that development, and treat people afflicted with kidney diseases.

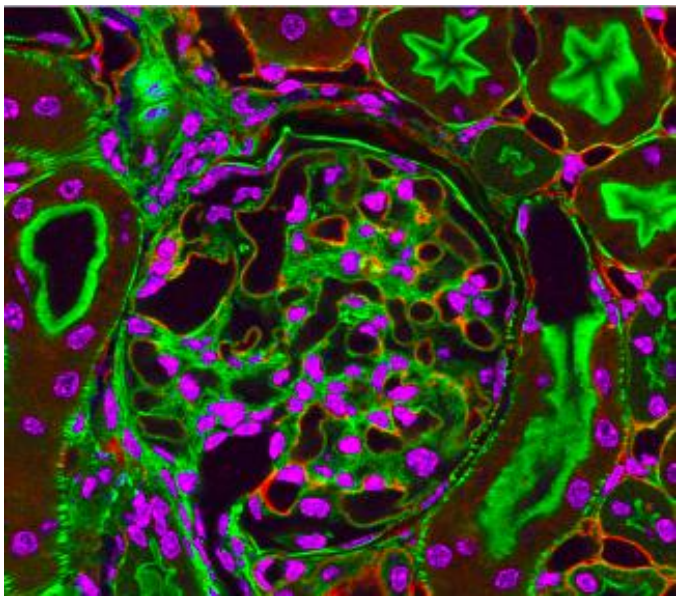

Figure 70. Photograph of kidney tissue, taken using fluorescent light microscopy. Credit: Tom Deerinck and Mark Ellisman, National Center for Microscopy and Imaging Research.

[1119] https://nei.nih.gov/about/goals-and-accomplishments/nei-research-initiatives/audacious-goals-initiative.
[1120] Goldberg JL, et al. *Invest Ophthalmol Vis Sci* 2016;57(3):1271-5. PMID: 26990163.
[1121] Vetter ML, et al. *Transl Vis Sci Technol* 2017;6(2):5. PMID: 28316878.
[1122] https://www.niddk.nih.gov/health-information/kidney-disease.
[1123] https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html.
[1124] https://nccd.cdc.gov/ckd/.

Understanding Prevalence, Risk Factors, and Underlying Biology

CKD is a major public health concern in the U.S. that can lead to end-stage renal disease. However, known risk factors have been unable to account for all the variability in CKD risk; therefore, research has expanded into examining environmental factors, such as metals, as a source of risk. NIH is funding a cohort study investigating the association between cumulative cadmium exposure and CKD in the San Luis Valley Diabetes Study cohort with longitudinal physiologic and behavioral data.[1125] Other pathophysiologic factors—including clinical information, diet, smoking, physical activity, family history, diabetes mellitus, and contributing medical factors—will be considered.

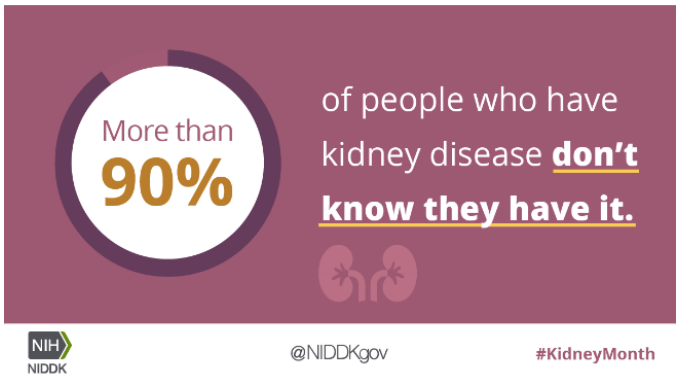

Figure 71. "More than 90 percent of people who have kidney disease don't know they have it" Infographic. Credit: NIDDK.

An NIEHS-funded study is aimed at determining whether exposure to heavy metals early in life contributes to renal toxicity in children and whether microRNAs (miRNAs) mediate metal nephrotoxicity.[1126] The study aims will be to (1) determine whether prenatal and early-life metal exposure predict childhood blood pressure or functional biomarkers in specific kidney regions, (2) apply a novel biostatistical approach to enable detection of metal-associated renal toxicity that is global or site-specific, and (3) examine the role of urinary miRNAs as biomarkers/mediators of metal–renal health relationships.

Another NIEHS-funded study is aimed at understanding the causes, mechanisms, and potential strategies for prevention of the international epidemic of CKD of unknown origin (CKDu).[1127] The central hypothesis of the study is that CKDu results from the combined effects of dehydration and exposure to nephrotoxins, due to enhanced reabsorption of nephrotoxins into the renal tubules during periods of recurrent dehydration. Access to a large population of sugarcane workers in cooperation with a major Guatemalan agribusiness will allow a study that characterizes and determines the contribution of occupational and environmental risk factors and that also evaluates subclinical kidney responses using biomarkers of early biological change in CKDu.

[1125] https://projectreporter.nih.gov/project_info_description.cfm?aid=9557512&icde=43187932.
[1126] https://projectreporter.nih.gov/project_info_description.cfm?aid=9767350&icde=43187932&ddparam=&ddvalue=&ddsub=&cr=10&csb=FY&cs=DESC&pball=.
[1127] https://projectreporter.nih.gov/project_info_description.cfm?aid=9432455&icde=43187932.

NIDDK-supported studies in mice have challenged long-standing views by shedding light on complex relationships between kidney physiology, salt intake,[1128] water balance, and hypertension.[1129] Findings from these studies provided important insights into the mechanisms by which the body maintains water balance in response to salt intake and could generate novel therapeutic approaches for reducing the risk of hypertension.

NIDDK-supported scientists reported that from young adulthood to old age, healthy adults lose about half of their nephrons—the basic functional unit of the kidney.[1130] Findings from this study could inform clinical guidelines for diagnosing kidney disease, helping to ensure that the disease is not over-diagnosed in older adults or under-diagnosed in younger adults.

NIDDK continued to support the Chronic Renal Insufficiency Cohort Study,[1131] which will evaluate the long-term cardiovascular risk and outcomes of approximately 5,500 men and women with CKD, the largest cohort study of CKD undertaken. The Chronic Kidney Disease in Children study of more than 500 children with mild to moderately decreased kidney function is (1) investigating risk factors for further kidney function decline, (2) closely monitoring brain development, (3) identifying risk factors for heart disease, and (4) determining long-term effects of poor growth in this group.[1132] The study has identified several risk factors for pediatric kidney disease, as well as early manifestations of disease. The Chronic Kidney Disease in Children Study has been renewed through 2018 and has expanded to allow the recruitment of additional patients.[1133, 1134]

African Americans have higher rates of incident end-stage renal disease than European Americans. The identification of *APOL1* kidney disease risk gene variants, which are among the only known genetic factors contributing to this health disparity and are found primarily in African Americans, is arguably the most important discovery about the pathogenesis of CKD over the past few decades. The NIDDK-supported *APOL1* Long-term Kidney Transplantation Outcomes Research Network was established to design and conduct studies of a prospective longitudinal cohort to determine the impact of *APOL1* genetic variants as susceptibility factors in U.S. kidney transplant recipients who received kidneys from African American donors.[1135] Related, a new NIDDK-supported study has found that levels of the protein suPAR in the blood can help predict whether kidney function will deteriorate in people with high-risk *APOL1* genetic variants, suggesting that modifying suPAR could be a possible therapeutic approach to treating CKD in individuals of recent African ancestry. [1136]

A growing consensus suggests that CKD and acute kidney injury (AKI) are heterogeneous disorders that contain specific subgroups that are driven by different disease pathways. Thus, a better understanding of

[1128] Kitada K, et al. *J Clin Invest* 2017;127(5):1944-59. PMID: 28414295.
[1129] Stegbauer J, et al. *JCI Insight* 2017;2(7):e92720. PMID: 28405625.
[1130] Denic A, et al. *J Am Soc Nephrol* 2017;28(1):313-20. PMID: 27401688.
[1131] http://www.cristudy.org/Chronic-Kidney-Disease/Chronic-Renal-Insufficiency-Cohort-Study/.
[1132] https://statepi.jhsph.edu/ckid/.
[1133] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-505.html.
[1134] https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-17-502.html.
[1135] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-025.html.
[1136] Hayek SS, et al. *Nat Med* 2017;23(8):945-53. PMID: 28650456.

disease heterogeneity will likely inspire the development of more effective individualized treatment options. NIDDK released an initiative to establish the Kidney Precision Medicine Project,[1137] which aims to ethically obtain and evaluate human kidney biopsies from participants with AKI or CKD; create a kidney tissue atlas; define disease subgroups; and identify critical cells, pathways, and targets for novel therapies.[1138] Additional technology development will be supported by small business programs.

It has not been clear whether gestational diabetes, like other forms of diabetes, confers CKD risk for women after pregnancy. Intramural researchers at NICHD analyzed data from a large cohort of women in Denmark who were pregnant during the years 1996–2002. They found that 9–16 years after pregnancy in which GDM occurred, tests of women's kidney function were significantly more likely to indicate early stages of renal impairment, compared with women with no history of GDM.[1139]

NIDDK-supported researchers discovered 24 new regions of the genome that are associated with kidney function or development and have confirmed 29 other genomic areas that were previously identified.[1140] These findings have generated numerous potential targets for therapeutic strategies to improve kidney health.

Anhydramnios is the complete, or nearly complete, lack of amniotic fluid surrounding the developing fetus in the uterus. Lack of amniotic fluid can cause devastating complications for the fetus, including severe skeletal structural abnormalities or stillbirth, as well as incomplete lung development, which can prove fatal in a newborn. Thus far, no standardized approaches exist to manage such cases, especially if anhydramnios is secondary to absence of fetal kidneys or abnormalities of the urinary tract in the fetus. Researchers and clinical experts were invited to a conference at NICHD where they reviewed the current knowledge and gaps in scientific understanding of anhydramnios in the context of fetal kidney abnormalities.[1141] They assessed the benefits and risks of currently used clinical interventions, postnatal and long-term outcomes in children with kidney abnormalities identified before birth, and ethical aspects of decisions about maternal-fetal interventions for the condition and its complications. Published workshop findings suggested priority areas for research, including research to better understand how amniotic fluid is produced and cleared, as well as to develop markers for assessing fetal kidney function.

NICHD-supported researchers reported on their efforts to identify genes responsible for the kidney defects in DiGeorge syndrome, a rare genetic disorder that can disrupt multiple organ systems, including the heart, brain, and kidneys. DiGeorge syndrome is caused by deletions in a small region of chromosome 22. The researchers found that patients with kidney defects typically had a deletion that included the gene *CRKL*.[1142] These findings are a step toward determining genetic causes and identifying potential therapeutic targets for patients with DiGeorge syndrome.

[1137] https://kpmp.org/.
[1138] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-028.html.
[1139] Rawal S, et al. *Diabetes Care* 2018;41(7):1378-84. PMID: 29728364.
[1140] Pattaro C, et al. *Nat Commun* 2016;7:10023. PMID: 26831199.
[1141] Moxey-Mims M and Raju TNK. *Obstet Gynecol* 2018;131(6):1069-79. PMID: 29742659.
[1142] Lopez-Rivera E, et al. *N Engl J Med* 2017;376(8):742-54. PMID: 28121514.

Despite therapeutic advances, kidney disease still has a significant impact on prognosis and quality of life for patients with systemic lupus erythematosus (SLE). Researchers funded by NIAMS used a mouse model of lupus nephritis to demonstrate that estrogen signals through estrogen receptor alpha on immune cells and renal cells, causing a shift in metabolic pathways that leads to progression of severe kidney damage.[1143] Parallel observations with SLE patients show that these results may be translated to human disease and shed light on the influence of hormonal factors in lupus disease progression. Although further studies are warranted, the insights from these current findings could lead to approaches for treating or preventing lupus nephritis.

NIEHS is building on recent efforts by convening an international workshop in 2019 on CKD of uncertain or unknown etiology. The disease—which affects largely otherwise-healthy young males—poses a notable burden in Sri Lanka, El Salvador, Guatemala, Nicaragua, and India. The partnership for this workshop includes NIEHS, NIDDK, the Consortium on the Epidemic of Nephropathy in Central American and Mexico, and the Pan American Health Organization.[1144] NIEHS also supports (with other ICs) the Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award. This program supports institutional research training programs in chronic, non-communicable diseases in LMICs.

Improving Treatment and Prevention

A Learning Healthcare System is a partnership in which clinical practice addresses a pragmatic trial research question, and the trial results inform practice. Recently, a pragmatic trial was completed by clinical investigators supported by NCATS; the investigators compared IV fluid administration with balanced crystalloids to IV fluid administration with saline to inform clinical practice.[1145] Both fluids have been used in critically ill adults for decades without knowing which treatment resulted in better clinical outcomes. Researchers studied 15,802 critically ill adults and found the use of balanced crystalloids for IV fluid administration lowered the rate of death from any cause, new renal-replacement therapy, and persistent renal dysfunction, compared to the use of saline.

A report from the Systolic Blood Pressure Intervention Trial (SPRINT)—supported by NHLBI, NIDDK , and others—found that in people who do not have CKD, an intensive blood pressure control regimen increases risk of declining kidney function; this risk is generally outweighed by a reduced risk for cardiovascular events and death.[1146] These findings, which add to those from other SPRINT studies, could help provide valuable insights that inform decisions made by patients and health care providers.

Because kidney transplantation is one of only two treatment options for kidney failure, research to improve its success with kidneys provided by living donors has been a high priority for NIDDK. NIDDK-supported scientists reported a survival benefit for people who received kidney transplants from

[1143] Corradetti C, et al. *J Immunol* 2018;200(2):512-22. PMID: 29237779.
[1144] https://www.niehs.nih.gov/research/programs/geh/partnerships/index.cfm.
[1145] Semler MW, et al. *N Engl J Med* 2018;378(9):829-39. PMID: 29485925.
[1146] Beddhu S, et al. *Ann Intern Med* 2017;167(6):375-83. PMID: 28869987.

human leukocyte antigen (HLA)-incompatible live donors compared with either those remaining on the kidney transplant waiting list or those who received kidney transplants from immune system–compatible deceased donors.[1147]

Kidney stones are one of the most common disorders of the urinary tract; larger stones may get stuck along the lower urinary tract and block the flow of urine, causing severe pain and/or bleeding. To improve kidney stone treatment, NIDDK-supported researchers developed new ultrasonic propulsion technology that can reposition kidney stones and facilitate stone fragment passage in people.[1148] A separate report from the NIDDK-supported Study of Tamsulosin for Urolithiasis in the Emergency Department clinical trial found that the drug tamsulosin, frequently used in the emergency room to treat people with urinary stone disease, has no benefit if the stones are larger than a certain size.[1149]

The NIDDK-supported Urinary Stone Disease Research Network (USDRN) is conducting research on urinary stones (kidney stones) in adults and children in order to learn more about who forms kidney stones, what the best treatments are, and how to prevent stones from forming.[1150] The USDRN launched the Prevention of Urinary Stones with Hydration (PUSH) study, which is currently recruiting participants. PUSH uses financial incentives, coaching, and new technology—smart water bottles—to encourage participants to drink more water.

AKI occurs in approximately 25 percent of children admitted to intensive care units. Among children who have cardiac surgery, rates of AKI are even higher, and AKI is associated with increased health problems and even death. Acetaminophen (marketed under the brand name Tylenol) is a well-established drug used to reduce pain and fever. Prior research has suggested that acetaminophen might help prevent AKI. Analyzing data from children who underwent surgery in the years 2008–2016, NICHD-supported researchers found that children who were given acetaminophen in the first 48 hours immediately following surgery may have a lower rate of AKI.[1151]

An NIDDK-supported study has established a correlation between the level of fibroblast growth factor-23 in the blood of people with CKD, measured over time, and the risk of death.[1152] This research could alert physicians to the need for improved care for these individuals.

To investigate whether medications and treatment approaches developed over the past 40 years have reduced the likelihood of renal failure in patients with SLE, NIAMS intramural researchers reviewed the published medical literature on the risks of renal failure in adults with SLE from 1970 to 2015.[1153] The risk of kidney failure decreased during the 1970s and 1980s, and plateaued in the mid-1990s. An increase in risk of kidney failure was observed in the 2000s, which is likely due to a specific subtype of aggressive

[1147] Orandi BJ, et al. *N Engl J Med* 2016;374(10):940-50. PMID: 26962729.
[1148] Harper JD, et al. *J Urol* 2016;195(4 Pt 1):956-64. PMID: 26521719.
[1149] Meltzer AC, et al. *JAMA Intern Med* 2018;178(8):1051-7. PMID: 29913020.
[1150] https://usdrn.org/.
[1151] Van Driest SL, et al. *JAMA Pediatr* 2018172(7):655-63. PMID: 29799947.
[1152] Isakova T, et al. *J Am Soc Nephrol* 2018;29(2):579-90. PMID: 29167351.
[1153] Tektonidou MG, et al. *Arthritis Rheumatol* 2016;68(6):1432-41. PMID: 26815601.

kidney inflammation. The results suggest that treatment advances have improved kidney outcomes for patients with SLE. However, the improvement stalled since the mid-1990s, either because the effectiveness of current treatments has been reached or due to a lack of progress in the delivery systems for existing treatments.

Mental Health

Mental illnesses affect millions of Americans each year, affecting people of all ages, sexes, ethnic, racial, and socioeconomic groups. Nearly one in five U.S. adults live with a mental illness (46.6 million in 2017).[1154] Major depression is one of the most common mental disorders in the U.S, affecting more than 7.1 percent of adult in 2017.[1155] In addition, numerous other forms of chronic mental illnesses cause suffering among Americans, including anxiety, eating disorders, and bipolar disorder.[1156]

Mental illnesses are associated with suffering both for individuals with the disorders and for their families and caregivers. Mental illnesses result in billions of dollars of lost economic productivity and expenses, including costs for treatment. Mental illnesses can also significantly affect a person's life expectancy: Investigators funded by NIMH and NIGMS analyzed 203 studies from 29 countries across six continents and found that the median reduction in life expectancy among people with a mental illness was 10.1 years, relative to the life expectancy of the general population.[1157] NIH seeks to invest in research to understand, prevent, and treat chronic mental illnesses.

Understanding Prevalence, Risk Factors, and Underlying Biology

NIEHS-funded researchers are investigating bisphenol A (BPA) exposure, peripartum depression, and altered neural functioning in pregnant minority or low-income women.[1158] The study will assess the prevalence of depression-associated psychiatric problems in the last trimester; measure symptoms specific to peripartum depression at 3 months postpartum; and estimate the attributable risk of BPA exposure and psychosocial stress on diagnosed prenatal depression and peripartum depression at 3 months postpartum.

Some studies in animals have suggested that prenatal exposure to a type of antidepressant called selective serotonin reuptake inhibitors may lead to intellectual disability. Using parental information from national registers in Sweden, researchers looked at information on almost 180,000 children over 8 years. After the researchers accounted for confounding factors—such as parental age, parental education, and other

[1154] https://www.nimh.nih.gov/health/statistics/mental-illness.shtml.
[1155] https://www.nimh.nih.gov/health/statistics/major-depression.shtml.
[1156] https://www.nimh.nih.gov/health/statistics/index.shtml.
[1157] Walker ER, et al. *JAMA Psychiatry* 2015;72(4):334-41. PMID: 25671328.
[1158] https://projectreporter.nih.gov/project_info_description.cfm?aid=9687384&icde=43188395&ddparam=&ddvalue=&ddsub=&cr=8&csb=default&cs=ASC&pball=.

psychiatric conditions—they found no relationship between antidepressant use by pregnant women and intellectual disabilities in their children.[1159]

A study funded by The Ohio State University Center for Clinical and Translational Science—and conducted by the Center for Injury Research and Policy, the Center for Pediatric Trauma Research, and the Center for Suicide Prevention and Research at Nationwide Children's Hospital—looked at the mental health and social functioning of children after they were hospitalized for an injury.[1160] Researchers found that children hospitalized for an injury had on average a 63 percent increase in mental health diagnoses and a 155 percent increase in medications prescribed to treat a mental illness.[1161] For children, injuries that require hospitalization may have a lasting impact on mental health.

In 2018, NIMH released guidance encouraging stress biology research and establishing guidelines and priorities for potential applicants. NIMH encourages efforts that address a set of critical topics: (1) the resilience-to-susceptibility spectrum, (2) consideration of complex systemic interactions, (3) inclusion of both sexes and consideration of sex differences, (4) methods to speed translation, and (5) development of translatable biomarkers. Rigorous and realistic animal models of stress will allow comparisons with human studies and hold promise for identifying targets for intervention.[1162,1163]

The NIMH Psychoactive Drug Screening Program provides the research community with access to broad screening capabilities in the form of pharmacological and functional assays.[1164] The purpose is to stimulate innovative research and development efforts in the discovery of novel tools for basic research, small-molecule probes, ligands for neuroimaging, and potential therapeutic agents for the treatment of mental illnesses. The program utilizes state-of-the-art high-throughput screening of compounds in assays for a wide variety of central nervous system targets.

An NICHD FOA encourages research grant applications focusing on identification and management of behavioral symptoms and mental health conditions in individuals with intellectual disabilities.[1165] Specific areas of interest for this funding opportunity are (1) applications to develop and validate assessment tools that reliably identify behavioral symptoms or diagnose mental health conditions in individuals with intellectual disabilities and (2) applications studying the pharmacokinetics, safety, and efficacy of specific psychotropic medications for treatment of behavioral symptoms or mental health conditions in individuals with intellectual disabilities.

A new study funded by NIEHS is aimed at identifying distinct and common prenatal risk factors for autism and other psychiatric disorders (schizophrenia, attention deficit hyperactivity disorder) that have never

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[1159] Viktorin A, et al. *JAMA Psychiatry* 2017;74(10):1031-38. PMID: 28700807.
[1160] https://www.nationwidechildrens.org/newsroom/news-releases/2018/05/children-hospitalized-for-injury-have-increased-mental-health-needs.
[1161] Bushroe KM, et al. *J Pediatr* 2018;199:29-34.e16. PMID: 29747938.
[1162] https://grants.nih.gov/grants/guide/notice-files/NOT-MH-18-058.html.
[1163] https://www.nimh.nih.gov/about/director/messages/2018/moving-stress-research-forward.shtml.
[1164] https://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2017/the-nimh-psychoactive-drug-screening-program-pdsp.shtml.
[1165] https://grants.nih.gov/grants/guide/pa-files/par-18-766.html.

before been investigated in maternal sera during pregnancy in a single study of a large national birth cohort.[1166] This may offer the potential for prevention of autism and these other disorders by straightforward public health measures, including reduction of exposure to environmental contaminants and vitamin supplementation. These studies could also result in an improved understanding of how prenatal insults alter brain development in autism and other psychiatric disorders.

To better understand the magnitude of mental health problems experienced by transgender or gender non-conforming (TGNC) children (ages 3–9 years) and adolescents (ages 10–17 years), NICHD-supported researchers examined electronic medical records of 588 transfeminine (i.e., assigned male at birth but identified as female) and 745 transmasculine (i.e., assigned female at birth but identified as male) children and adolescents. Each study participant was matched to 10 male and 10 female cisgender participants with similar demographic characteristics. For all diagnostic categories, TGNC participants were more likely to experience mental health concerns than cisgender participants.[1167] Of special concern, both self-inflicted injury and suicidal thoughts were significantly higher in TGNC participants compared with the cisgender participants.

Adolescents living in areas surrounded by trees and other green vegetation have better mental health than those exposed to less greenery at home, according to new research supported by several NIH ICs.[1168] The study is one of the first to examine the relationship between natural environments and depressive symptoms in adolescents.

A top priority for NIMH is to understand the complex genetic landscape of mental illnesses, and a crucial step is understanding how genomic variation influences gene regulation. Co-led by NCI, NGHRI, and NIMH and supported by the NIH Common Fund, the Genotype-Tissue Expression Consortium researchers collected data from more than 53 different post-mortem tissue types from more than 950 donors and completed a detailed atlas documenting the stretches of human DNA that influence gene expression.[1169] This atlas is designed to help researchers understand the mechanisms by which genes are expressed in a variety of tissues and, ultimately, better understand how genes are misregulated in the context of illnesses.

NIMH developed a computational psychiatry program that fosters a novel, biologically based computational framework to identify and validate biomarkers and novel treatment targets relevant to the prevention, treatment, and recovery of mental illnesses.[1170] NIMH issued FOAs for sophisticated theory- and data-driven computational approaches to research the etiology and pathophysiology of mental illnesses using a dimensional framework.[1171] In addition, NIMH encourages computational approaches to

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[1166] https://projectreporter.nih.gov/project_info_description.cfm?aid=9551627&icde=43188521&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=.
[1167] Becerra-Culqui TA, et al. *Pediatrics* 2018;141(5). pii: e20173845. PMID: 29661941.
[1168] Bezold CP, et al. *J Adolesc Health* 2018;62(4):488- 95. PMID: 29273301.
[1169] https://www.nih.gov/news-events/news-releases/nih-completes-atlas-human-dna-differences-influence-gene-expression.
[1170] https://www.nimh.nih.gov/about/director/messages/2017/computational-neuroscience-deciphering-the-complex-brain.shtml.
[1171] https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-19-240.html.

develop back-translatable behavioral measures related to mental illnesses and computational methods for integrative analysis of genomic and single-cell data.[1172,1173]

In 2018, NIMH released a National Advisory Mental Health Council workgroup report providing recommendations to address the complexity inherent in genomic psychiatry, including (1) applying rigorous statistical methods, (2) focusing on unbiased genetic association studies, (3) examining all types of genetic variation, (4) expanding efforts beyond the Diagnostic and Statistical Manual of Mental Disorders, (5) including genetic and phenotypic variation across diverse human populations, (6) developing and sharing research resources, and (7) requiring robust, genomewide significance in selecting genes and gene variations for further study.[1174,1175] To support the use and uptake of these recommendations, NIMH released additional guidance for grant applicants, outlining factors NIMH considers when assessing human genetics research applications for the study of common genetic variation, rare genetic variation, and genetic syndromes.[1176]

NICHD-supported researchers showed that low blood levels of a biomarker called brain-derived neurotrophic factor (BDNF) were associated with depressive symptoms in a racially diverse cohort of pregnant women.[1177] Prior research demonstrating an association of BDNF and depression had largely excluded pregnant participants. In the current study with pregnant women, researchers supported by NICHD, NINR, and NCATS found that BDNF levels dropped considerably from the first through the third trimester; lower BDNF in the third trimester occurred with more severe depression; and Black women had higher BDNF levels throughout pregnancy.[1178] In addition, women delivering low versus healthy weight infants showed lower BDNF in the third trimester. As a biomarker, BDNF can serve as an important research tool in understanding basic mechanisms underlying postpartum depression, including a potential biological basis for racial and ethnic differences in women's risk of postpartum depression.

Researchers from the NIMH-supported Bipolar and Schizophrenia Network for Intermediate Phenotypes study examined key biological and behavioral measures linked to psychosis among a large cohort of individuals diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis.[1179] Using a computational approach that included measures of performance on planning and memory tasks, eye-tracking, inhibition, and brainwave responses to auditory stimuli, researchers discovered that participants clustered into three distinct psychosis-related biotypes independent of their traditional diagnostic categories. Other measures, such as social functioning, brain structure, and rates of psychosis-

[1172] https://grants.nih.gov/grants/guide/pa-files/PAR-17-252.html.
[1173] https://grants.nih.gov/grants/guide/pa-files/PAR-17-253.html.
[1174] https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/namhc-genomics-workgroup-research-recommendations-summary.shtml.
[1175] https://www.nimh.nih.gov/about/director/messages/2018/towards-a-genomic-psychiatry-recommendations-of-the-genomics-workgroup-of-the-namhc.shtml.
[1176] https://www.nimh.nih.gov/research/research-funded-by-nimh/policies/guidance-for-applicants-following-the-report-of-the-national-advisory-mental-health-council-workgroup-on-genomics.shtml.
[1177] Christian LM, et al. *Psychoneuroendocrinology* 2016;74:69-76. PMID: 27588702.
[1178] Clementz BA, et al. *Am J Psychiatry* 2016;173(4):373-84. PMID: 26651391.
[1179] https://www.nimh.nih.gov/news/science-news/2015/biomarkers-outperform-symptoms-in-parsing-psychosis-subgroups.shtml.

related illness and biomarker patterns in patients' first-degree relatives, showed that these biotypes were more distinct than the groupings based on traditional diagnostic categories.

NIMH supports research on youth at high risk for schizophrenia and psychosis. The North American Prodrome Longitudinal Study focuses on early-stage symptoms that emerge in some people who go on to develop schizophrenia, with a goal of informing the development of treatments that may delay or prevent the conversion to psychosis or minimize its impact.[1180] In addition, NIMH issued a FOA to support a large-scale initiative focused on testing the effectiveness of interventions that target individuals who are at high risk for or who have early psychosis.[1181–1183] Other NIMH efforts have shown that rapid treatment of first-episode psychosis leads to improved outcomes; current efforts hold promise to further improve outcomes.

Researchers from NIEHS found that neuronal activity in hippocampal area CA2, a brain region thought to regulate social memory, affects a form of electrical neuronal communication called gamma oscillations.[1184] Because gamma oscillations are known to be impaired in patients with schizophrenia, the finding suggests that CA2 may be involved in the pathophysiology of schizophrenia.

NIEHS is funding research using computational genomics to discover rare genetic variants that influence human complex traits, including two psychiatric disorders: bipolar disorder and schizophrenia.[1185] Identifying those rare variants is critical for both biology and human health, because it will elucidate the genetic basis of those disorders and facilitate development of treatment.

Exercise and antidepressants affect bone health in adolescent girls with anorexia nervosa. Excessive caloric restriction can lead to abnormalities in the endocrine system, with decreased muscle and bone mass. To assess how malnutrition and lifestyle affect bone health in anorexia, researchers compared 70 adolescent girls with anorexia and 132 normal-weight controls. The scientists found that in adolescents with anorexia, antidepressants may negatively affect bone mineral density, but exercise can positively influence bone mineral density.[1186] Although exercise had benefits on bone growth in girls with anorexia, they still had evidence of weaker bones and increased fracture risk compared with healthy girls.

Improving Treatment and Prevention

More than half of people who have a TBI will develop major depressive disorder within the first year after their injury. Many providers prescribe antidepressants, particularly selective serotonin reuptake inhibitors, to treat depression after a brain injury. NICHD-supported researchers studied one of these

[1180] http://campuspress.yale.edu/napls/.
[1181] https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-210.html.
[1182] https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-211.html.
[1183] https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-212.html.
[1184] Alexander GM, et al. *Elife* 2018;7. pii: e38052. PMID: 30387713.
[1185] https://projectreporter.nih.gov/project_info_description.cfm?aid=9521980&icde=43188521&ddparam=&ddvalue=&ddsub=&cr=18&csb=default&cs=ASC&pball=.
[1186] DiVasta AD, et al. *J Adolesc Health* 2017;60(2):229-32. PMID: 27939877.

drugs, sertraline, in patients who were depressed after TBI.[1187] Half of the participants received sertraline, and the other half received a placebo pill. After 12 weeks, depression in both groups had improved, with the sertraline patients doing no better than the patients who received the placebo. The results indicate that other treatments may be needed for people who experience major depression after TBI.

Working in collaboration with NIH and academic researchers, NCATS chemists played a critical role in isolating a specific metabolite of ketamine, a drug that can fight depression.[1188–1191] An intramural investigator at NCATS, together with collaborators, found that this metabolite reverses depression-like behaviors in mice without triggering the undesirable side effects of ketamine that limit its clinical utility.[1192–1195] NIH's collective efforts exemplify NCATS' mission, showing how a collaborative team science approach can help advance the translational process in ways that help get more treatments to more patients more quickly.

The Mental Health Research Network (MHRN) is NIMH's prototype of a learning health care system that involves 13 health care systems that reach approximately 13 million beneficiaries nationwide. Twenty-three studies, in various stages of completion, have leveraged the MHRN infrastructure.[1196] Some MHRN members participate in practical clinical trials via the NIH Common Fund Health Care Systems Research Collaboratory, one of which represents the largest U.S. intervention trial aimed at preventing suicide attempts.[1197,1198] Study investigators are using an automated EHR strategy to identify patients reporting high suicide ideation; individuals who are identified as high risk for suicide are randomly assigned to one of three evidence-based interventions to reduce suicidal ideation and prevent suicide attempts.

The NIMH Emergency Department Safety Assessment and Follow-up Evaluation (ED-SAFE) project demonstrated that ED-initiated interventions could reduce subsequent suicidal behavior among high-risk adult ED patients, and a follow-on study aims to examine the sustainability of successfully implemented universal suicide risk screening.[1199] The NIMH Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) study investigators generated a 2-minute, personally tailored, computerized screening tool for EDs to assess youth suicide risk, and these researchers are following adolescents at elevated risk for suicide to identify warning signs for suicide attempts.[1200] NIMH continues to support suicide prevention research among vulnerable populations within specific communities, including collaborative research

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[1187] Fann JR, et al. *J Head Trauma Rehabil* 2017;32(5):332-42. PMID: 28520672.
[1188] https://ncats.nih.gov/chemtech/projects/active/ketamine.
[1189] Zanos P, et al. *Nature* 2016;533(7604):481-6. PMID: 27144355.
[1190] Highland JN, et al. *J Psychopharmacol* 2018:269881118812095. PMID: 30488740.
[1191] Moaddel R, et al. *Psychopharmacol* 2018;235(10):3017-30. PMID: 30116859.
[1192] https://www.nih.gov/news-events/news-releases/ketamine-lifts-depression-byproduct-its-metabolism.
[1193] https://www.nih.gov/news-events/news-releases/ketamine-lifts-depression-byproduct-its-metabolism.
[1194] Morris PJ, et al. *Org Lett* 2017;19(17):4572-5. PMID: 28829612.
[1195] Zanos P, et al. *Pharmacol Rev* 2018;70(3):621-60. PMID: 29945898.
[1196] http://www.hcsrn.org/en/Collaboration/Consortia/mhrn.html.
[1197] https://commonfund.nih.gov/hcscollaboratory.
[1198] https://rethinkingclinicaltrials.org/.
[1199] https://www.nimh.nih.gov/news/science-news/2017/emergency-departments-could-play-significant-role-in-reducing-suicide-attempts.shtml.
[1200] https://www.nimh.nih.gov/archive/news/2014/personalized-screen-to-id-suicidal-teens-in-14-ers.shtml.

hubs that aim to reduce the burden of suicide among American Indian and Alaska Native youth in both urban and rural settings.[1201] In addition, NIMH supports several Zero Suicide projects,[1202] and partners with the NIH OBSSR and the National Institute of Justice within the U.S. Department of Justice to support a study to evaluate the effectiveness of an evidence-based safety planning intervention to reduce suicide events among persons recently released from incarceration.[1203,1204]

NIMH promotes science education and literacy through its partnerships with professional and advocacy communities.[1205] The NIMH Outreach Partnership Program is a nationwide initiative designed to increase the public's access to science-based mental health information through partnerships with national and state organizations. The NIMH Alliance for Research Progress convenes NIMH leadership and mental health advocates from national voluntary organizations representing individuals with mental illness.[1206] In addition, the NIMH Professional Coalition for Research Progress convenes senior leaders and representatives from national professional organizations with an interest in NIMH research.[1207]

NIMH launched the *Discover NIMH* YouTube video series,[1208] hosted a Facebook live event on suicide prevention,[1209] and hosted Twitter chats on a variety of topics, including disruptive mood dysregulation disorder and severe irritability, African American men's mental health, seasonal affective disorder, and teen depression.[1210] These events were widely followed, allowing NIH experts to engage with millions of people on NIMH's social media channels.[1211] In 2017, the NIMH enterprise Twitter account surpassed one million followers, and NIMH established the NIMH Director's Twitter account.

In 2016, NIMH launched the Director's Messages section of its website to provide a venue for the Director to share information about mental illnesses and NIMH-supported research.[1212] In 2017, NIMH conducted a website usability study to inform ongoing improvements to its website, including content reorganization and informative visual displays.[1213] NIMH also undertook an effort to refresh its mental illness statistics webpages by consolidating information, updating information and sources, and introducing interactive figures.[1214] In addition, NIMH updated several health topics pages, fact sheets, and brochures to provide

[1201] https://www.nimh.nih.gov/news/science-news/2018/hubs-help-native-american-communities-address-youth-suicide.shtml.
[1202] https://grants.nih.gov/grants/guide/notice-files/NOT-MH-17-031.html.
[1203] https://www.nimh.nih.gov/news/science-news/2015/embracing-the-spirit-of-reducing-suicide.shtml.
[1204] https://www.nimh.nih.gov/about/director/messages/suicide-prevention.shtml.
[1205] https://www.nimh.nih.gov/outreach/index.shtml.
[1206] https://www.nimh.nih.gov/outreach/alliance/index.shtml.
[1207] https://www.nimh.nih.gov/outreach/coalition/index.shtml.
[1208] https://www.youtube.com/channel/UCkv4SxLREmIKoUYzabJX4dQ.
[1209] https://www.facebook.com/nimhgov/.
[1210] https://www.nimh.nih.gov/news/social-media/twitter/index.shtml.
[1211] https://www.nimh.nih.gov/news/social-media/index.shtml.
[1212] https://www.nimh.nih.gov/about/director/messages/index.shtml.
[1213] https://www.nimh.nih.gov/index.shtml.
[1214] https://www.nimh.nih.gov/health/statistics/index.shtml.

the latest information to stakeholders, including individuals living with mental illnesses, their families, mental health service providers, voluntary community organizations, and others.[1215]

In 2017, NIMH released a National Advisory Mental Health Council workgroup report addressing how new mobile health (mHealth) technologies can be used to advance both clinical research and practice. NIMH supports a wide variety of mHealth and telehealth research efforts including those that aim to: develop and test online and telephone strategies to prevent and treat depression in pregnant women before and after childbirth; develop a telehealth system that provides autism diagnostic assessments through the use of remote diagnostic clinicians; develop and test an online tool to facilitate early detection of tardive dyskinesia, a common and debilitating side effect of antipsychotic use; promote HIV testing and care engagement; and, support data collection and evidence-based decision making in LMICs.[1216] For example, findings from NIMH-funded studies demonstrated that a telecoach plus mood manager outperformed a self-directed mood manager for improving treatment adherence, and telehealth had longer sustained positive outcomes than in-person intervention for low-income homebound older adults with depression.[1217,1218]

Muskuloskeletal and Skin Diseases

Many different types of musculoskeletal and skin diseases affect millions of Americans. For example, 24.5 percent of women over age 65 have osteoporosis in the neck or spine.[1219] Psoriasis, a chronic autoimmune skin disease, affects more than 6.7 million Americans.[1220] Musculoskeletal and skin diseases often occur as complications from other conditions, compounding the impact on a person's quality of life and health. NIH, with NIAMS as the lead IC in this research area, investigates the basic mechanisms behind these diseases and conditions, explores how and why they develop, and searches for new ways to treat and prevent them.

Of particular note, NIH supports a broad range of research into muscular dystrophies (MDs)—a group of more than 30 genetic diseases characterized by progressive degeneration of the skeletal muscles. As required by the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84) and subsequent legislation, NHLBI, NIAMS, NICHD, and NINDS support a total of six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs).[1221] The centers promote collaborative basic, translational, and clinical research and provide important resources that can be used by the national MD research community. The centers also provide outstanding environments for the training of new scientists, and center investigators are expected to

[1215] https://www.nimh.nih.gov/health/topics/index.shtml.
[1216] https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/opportunities-and-challenges-of-developing-information-technologies-on-behavioral-and-social-science-clinical-research.shtml.
[1217] Mohr DC, et al. *PLoS One* 2013;8(8):e70086. PMID: 23990896.
[1218] Choi NG, et al. *Depress Anxiety* 2014;31(8):653-61. PMID: 24501015.
[1219] https://www.cdc.gov/nchs/fastats/osteoporosis.htm.
[1220] https://www.cdc.gov/psoriasis/.
[1221] https://www.wellstonemdcenters.nih.gov/.

participate in community outreach efforts with the patient and advocacy communities. More information on these centers is available in Chapter 4.

Understanding Prevalence, Risk Factors, and Underlying Biology

NIAMS is building on more than 15 years of investments to identify and validate biomarkers for osteoarthritis (OA), the most common form of arthritis. Through public–private partnerships among NIAMS and other NIH ICs, FNIH, and pharmaceutical companies, Osteoarthritis Initiative investigators established a public-domain resource to discover, evaluate, and validate biomarkers for OA. In August 2018, the FNIH Biomarkers Consortium, NIAMS, and other public and private partners launched PROGRESS OA: Clinical Evaluation and Qualification of Osteoarthritis Biomarkers, a project that builds on earlier discoveries and seeks regulatory qualification through the FDA of imaging and blood biomarkers that predict joint damage from OA over time.[1222] This qualification could enhance biomarker usage in drug development and pave the way for improved treatment, prevention, and diagnosis of this common joint disorder.

NIA-supported research also looked at the role of senescent cells in OA.[1223] The researchers found that senescent cells accumulate at the site of injury, leading to symptoms of osteoarthritis, and that selective elimination of those cells attenuated the development of osteoarthritis and reduced pain. These findings indicate senescent cells as a possible therapeutic target for treating degenerative joint disease.[1224]

While lower limb MRI is being used as a biomarker in clinical trials to measure progression of DMD, the tool is useful only for boys who retain the ability to walk. Once a patient with DMD is confined to a wheelchair, the leg muscles are almost completely replaced by fat and nonfunctioning connective tissue. Investigators demonstrated that MRI of the arm and shoulder can be followed to track disease progression and response to an intervention during clinical studies involving older patients in the later stages of disease.[1225] This could dramatically expand the number of individuals who could participate in clinical trials.

More than 10 million people nationwide have osteoporosis, in which bones become susceptible to fracture. Osteoporosis tends to run in families, and genetics is known to play an important role in bone mineral density, a major risk factor for fractures. Scientists have already identified many genetic factors associated with bone mineral density. These factors, however, likely represent just a small fraction of the underlying genetic variance. A large-scale, international genomic study to identify novel genetic variants affecting bone mass led to the discovery that an unexpected gene, *EN1,* plays a central role in regulating

[1222] https://fnih.org/news/announcements/measuring-knee-osteoarthritis?bblinkid=107211083&bbemailid=9023186&bbejrid=695387184.
[1223] https://www.nia.nih.gov/health/osteoarthritis.
[1224] Jeon OH, et al. *Nat Med* 2017;23(6): 775-81. PMID: 28436958.
[1225] Willcocks RJ, et al. *J Neurol* 2017;264(1):64-71. PMID: 27778157.

bone mineral density and is a critical gene in bone physiology.[1226] These results provide insights into the genetics underlying osteoporosis and may lead to new ways to prevent bone loss and fractures.[1227]

Parathyroid hormone (PTH) therapy is used to treat osteoporosis in people who are at high risk of fractures (e.g., postmenopausal women) by stimulating new bone formation. Although the downstream PTH signaling events in bone cells are well characterized, how this signaling in osteocytes is linked to gene expression changes remains unknown. An international team of researchers supported by NIAMS identified the enzyme salt-inducible kinase 2 (SIK2) and its downstream signaling molecules as potential drug targets for strategies to boost bone mass.[1228] Follow-up cell and mouse studies showed that small-molecule inhibitors of SIK2 hold promise as new drug candidates. The compounds mimic the bone-building properties of teriparatide—an osteoporosis drug derived from PTH that stimulates new bone formation. In addition, one of the compounds reduced the number of bone-destroying osteoclast cells—a welcome, albeit unexpected, effect for enhancing bone formation that may overcome teriparatide's limitations and allow longer-term use.

NIH researchers are contributing to the basic knowledge of how different regions of DNA regulate gene expression. Some are focusing on enhancers, which are short regions of DNA that produce noncoding RNAs (i.e., enhancer RNAs, or eRNAs) that contribute to gene activation. NIAMS intramural researchers demonstrated that a muscle-specific eRNA recruits a protein called cohesin to regulate expression of distant genes.[1229] This study explains one step in muscle-cell maturation and adds to a growing body of work demonstrating long-range interactions between eRNAs and distant genes located on other chromosomes.

RNA, once thought to exist only within cells, is now known to be exported from cells and to play a role in newly discovered mechanisms of cell-to-cell communication. The NIH Common Fund's Extracellular RNA Communication program aims to discover fundamental biological principles of extracellular RNA (exRNA) and to explore the possibility of using exRNAs as disease biomarkers or therapeutic molecules. Researchers from the NIH Common Fund's Extracellular RNA Communication program have identified an RNA biomarker signature in urine that may be used to diagnose or monitor patients with MD.[1230] This biomarker could eliminate the need for invasive muscle biopsies to diagnose MD and be used to track response to drug treatments targeting the RNA splicing process.

[1226] Zheng HF, et al. *Nature* 2015;526(7571):112-7. PMID: 26367794.
[1227] https://www.nih.gov/news-events/nih-research-matters/bone-risks-linked-genetic-variants.
[1228] Wein MN, et al. *Nat Commun* 2016;7:13176. PMID: 27759007.
[1229] Tsai PF, et al. *Mol Cell* 2018;71(1):129-41.e8. PMID: 29979962.
[1230] Antoury L, et al. *Nat Commun* 2018;9(1):3906. PMID: 30254196.

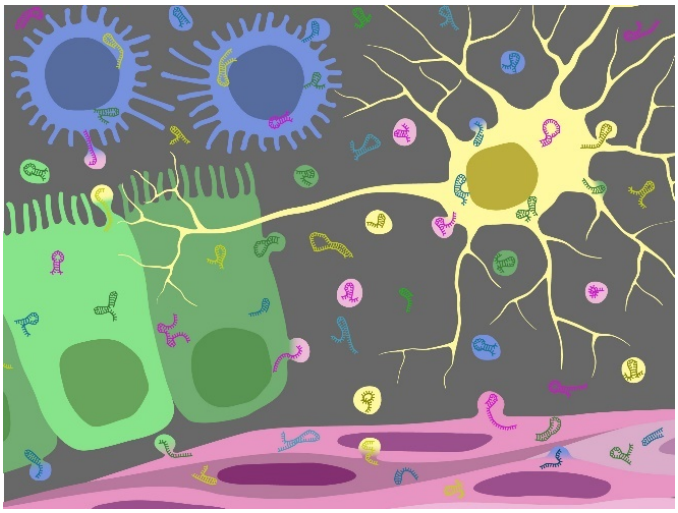

Figure 72. The NIH Common Fund's Extracellular RNA Communication program. Credit: NIH.

Inappropriate expression of a gene called *Dux4* in muscle cells causes cell death and leads to facioscapulohumeral MD (FSHD). *Dux4* is expressed in sperm and egg cells and plays an essential role in the development of embryos shortly after fertilization, after which time it is silenced. Researchers identified two complexes that are responsible for silencing *Dux4* in normal cells and another protein family that contributes to *Dux4*'s upregulation in affected muscle and the spreading of its toxic gene products to other nearby nuclei within the muscle cell.[1231] These new targets control the toxic expression of *Dux4* and suggest a new class of therapeutics for FSHD.

Only about 400 cases are known of the bone disorder melorheostosis, which is characterized by pathological thickening of the bones and is also known as dripping candle wax bone disease. Whereas most adults have the problem of weakening bones as they grow older, patients with melorheostosis have the opposite problem, because some of their bones are very hard and still growing. NICHD intramural researchers worked with NIAMS researchers to study 15 patients from around the world to determine the genetic basis for this disease.[1232] They uncovered fundamental information about the role of a cancer-related gene, *MAP2K1,* in the metabolic pathways of normal bone.[1233]

[1231] Campbell AE, et al. *Elife* 2018;7. pii: e31023. PMID: 29533181.
[1232] https://www.nichd.nih.gov/newsroom/news/041118-bone-disorder.
[1233] Kang H, et al. *Nat Commun* 2018;9(1):1390. PMID: 29643386.

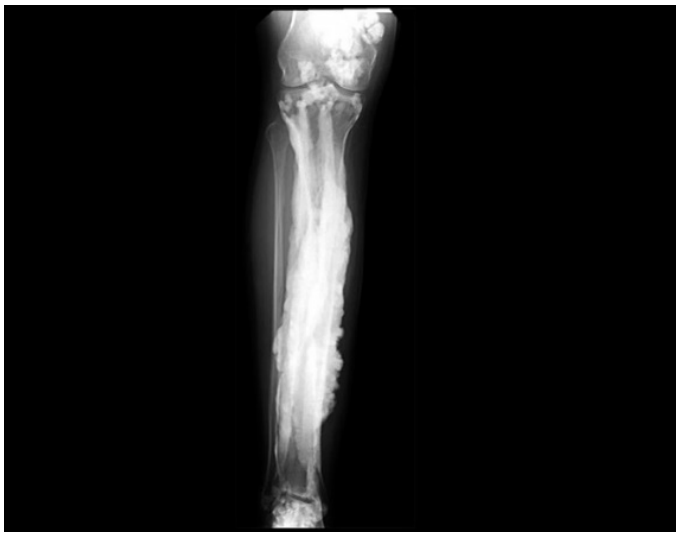

Figure 73. An X-ray image of a patient with melorheostosis shows excess bone formation, likened to dripping candle wax. Credit: NIH.

New research provides insight into the role that abnormal joint mechanics play in the development of arthritis following an anterior cruciate ligament tear and, ultimately, could provide a framework for the design of strategies to prevent post-traumatic OA. Compared with patients who had anterior cruciate ligament reconstruction but did not develop OA within 5 years, patients who had radiographic knee OA 5 years after anterior cruciate ligament reconstruction were more likely to have walked with a reduced range of motion 6 months after surgery.[1234] Altered movement patterns are common months after anterior cruciate ligament reconstruction and likely contribute to articular cartilage breakdown and may need to be corrected to allow the repaired knee to safely withstand the demands of sports, leisure, and occupational activities. Given that healthy movement patterns can be restored through rehabilitation, the study results also highlight the potential that post-traumatic OA could be prevented after anterior cruciate ligament injury.

Although a great deal is known about how open wounds on the skin's surface heal, relatively little is known about what happens when a wound is below the skin's surface. NIAMS-supported researchers developed a new imaging technique to track the movement and fate of living cells in mice. Using this method, they demonstrated that the skin has mechanisms to heal injuries that occur below its surface.[1235] This new technology will enable further research to understand wound healing in tissues deeper in the body.

NIAMS-funded investigators discovered that cells involved in recovery from deep cuts—which often involves scarring—can also become fat cells that underlie healthy skin tissue.[1236] Although little is known about how to direct skin repair toward regenerating normal skin instead of scarring, hair follicles may hold a clue because they seem to be a prerequisite for the formation of these new fat cells. This and related

[1234] Wellsandt E, et al. *J Orthop Res* 2017;35(3):651-6. PMID: 27747918.
[1235] Brown S, et al. *Nature* 2017;548(7667):334-7. PMID: 28783732.
[1236] Plikus MV, et al. *Science* 2017;355(6326):748-52. PMID: 28059714.

findings are opening new avenues of research, which could lead to novel treatment strategies for severe scarring and fibrotic diseases.

Itch is a common condition, and scratching in response to an itch is a contagious behavior in mice, as well as in people.[1237] Recent research into the brain changes that occur when one mouse sees another scratching has uncovered a neurotransmitter that is responsible for contagious itch.[1238] Although it is too early to tell what the immediate impact of the findings will be, the discovery opens the possibility of novel interventions to treat chronic itch that target the brain directly.

Using zebrafish engineered to produce signals that change color under different conditions, investigators demonstrated how adult zebrafish can perfectly regenerate the skeleton of an amputated fin. They discovered that a pool of cells at the outermost layer of the skin migrates over newly formed bones and produces a protein—known as Sonic hedgehog—that interacts with bone-generating cells and directs them to regenerate branched skeletons like those comprising the original fin.[1239] In other words, with the right signals, bone- and skin-precursor cells can work together to restore severely damaged zebrafish bone to its original structure. This finding is important, because—although healthy human bone heals most of the time—some fractures do not repair on their own.

Researchers isolated stem cells from fat, grew them to make thin sheets, and tested the cells' ability to stimulate flexor tendon healing under different conditions. Using an innovative system to deliver a tendon growth–promoting factor in combination with the cell sheets, they compared four repair procedures with normal tendon in a large-animal model.[1240] Their results at 2 weeks post-repair demonstrated that fat stem cells in combination with a tendon growth–promoting factor speed up tendon repair and best resemble the normal tendon. Building on these promising results, the researchers are continuing to study long-term outcomes before testing this approach in people.

Skeletal muscle normally repairs and regenerates unless it is diseased or severely damaged, and engineering functional skeletal muscles that are large enough to be therapeutically useful in people is challenging. A 2018 *Nature Communications* paper reports successful production of enough iPSCs to generate 3-D functional human skeletal muscles.[1241] Researchers demonstrated the ability to differentiate immature stem cells into satellite-like cells that make muscle, identified conditions that allowed these cells to form 3-D muscle bundles, and showed that these muscle bundles can generate force and are responsive to electrical and chemical stimulations. Furthermore, they implanted these muscle bundles into a mouse model, where the bundles incorporated into the host mouse tissues.

One of the most significant challenges remaining for iPSC transplantation for treating muscle diseases is the ability to get corrected iPSCs to engraft into skeletal muscle and effectively replace the lost mature muscle with healthy tissue. In 2018, researchers described an iPSC-based method that led to a more-than-

[1237] https://www.nih.gov/news-events/nih-research-matters/socially-contagious-itching-hardwired-into-brain.
[1238] Yu YQ, et al. *Science* 2017;355(6329):1072-6. PMID: 28280205.
[1239] Armstrong BE, et al. *Development* 2017;144(7):1165-76. PMID: 28351866.
[1240] Gelberman RH, et al. *Clin Orthop Relat Res* 2017;475(9):2318-31. PMID: 28462460.
[1241] Rao L, et al. *Nat Commun* 2018;9(1):126. PMID: 29317646.

10-fold improvement in the engraftment of human muscle stem cells into a model of DMD, compared with prior approaches.[1242] The technique, enabled by studies looking at normal human stem cell development, provides step-by-step instructions and proof of concept for a stem cell–based therapy for muscle diseases.

Improving Treatment and Prevention

The Paul D. Wellstone MDCRCs are designed to foster the translation of new scientific findings and technological developments into novel treatments for muscular dystrophies.[1243] The centers promote basic, translational, and clinical research and provide important resources that can be used by the national muscle biology and neuromuscular research communities. The MDCRCs also engage patients and patient advocates in educational programs. Centers include one or more scientific research resource cores that support the specific projects and serve as a resource for the international research community.

Mutations in the gene encoding dystrophin, a protein that maintains muscle integrity and function, cause DMD. Using an animal model, researchers tested whether delivering gene editing components to animals' muscles could restore the dystrophin protein.[1244] After the genetic material was delivered into skeletal muscle, dystrophin expression increased. The results of these experiments support the hypothesis that, with further development, gene editing approaches may prove useful for the treatment of DMD.

NIAMS-supported researchers have demonstrated a proof of principle that expression of small proteins, called viral proteins, interfering with antigen presentation, which impairs the presentation of proteins to the immune system for identification as self or non-self, can conceal a therapeutic dystrophin gene from the immune system.[1245] Nearly 30 percent of DMD patients have pre-existing immunity to dystrophin, suggesting that a significant fraction of this population may be unable to benefit from current gene therapy approaches in clinical trials. Methods based on viral proteins interfering with antigen presentation or related approaches could minimize the immune system's clearance of therapeutic proteins in a highly specific way; therefore, these methods would not require long-term—and potentially riskier—systemic suppression of the immune system.

NIAMS-supported investigators are also testing whether basic research advances in CRISPR-based technology, which allows precise targeting of specific genetic sequences, can be leveraged for new gene therapy treatments to correct the genetic defects underlying two of the most common muscular dystrophies. One group recently described an approach that, if adapted for humans and proven safe and effective, might be a treatment for FSHD.[1246] Another group is developing a related technique that theoretically could benefit up to 60 percent of the people who have DMD.[1247]

[1242] Hicks MR, et al. *Nat Cell Biol* 2018;20(1):46-57. PMID: 29255171.
[1243] https://www.nichd.nih.gov/research/supported/Pages/mdcrc.aspx.
[1244] Amoasii L, et al. *Science* 2018;362(6410):86-91. PMID: 30166439.
[1245] Shao W, et al. *Hum Mol Genet* 2018;27(4):601-13. PMID: 29272432.
[1246] Himeda CL, et al. *Mol Ther* 2016;24(3):527-35. PMID: 26527377.
[1247] Young CS, et al. *Cell Stem Cell* 2016;18(4):533-40. PMID: 26877224.

Researchers examined cell culture and mouse models to understand how glucocorticoids preserve muscle function in boys who have DMD. They found that weekly dosing upregulates two genes involved in muscle cell membrane repair, while daily dosing activates cell pathways that cause muscle to shrink and weaken.[1248] If the responses also occur in patients, this study could directly inform prescription instructions that would maximize the drugs' therapeutic benefit while minimizing negative side effects. This work could also extend beyond the muscular dystrophies, because approximately 1 percent of the entire U.S. population is treated chronically with glucocorticoids for other conditions.

Researchers developed a strategy to sequentially deliver the two molecules associated with stem cell differentiation for meniscal repair in a single dose—one was released within 5 days and the other over a period 36 days.[1249] Sequential treatment with the two molecules by the single-dose delivery resulted in superior healing of the meniscal inner layer as measured both in appearance and in function of in vitro bovine meniscus, as compared with untreated tissues or tissues exposed to either molecule alone. Animal experiments using the same integrated delivery approach also showed that the molecules could promote healing when delivered together. Single-dose delivery is minimally invasive and therefore better positioned for future clinical application; future work includes moving into large-animal models and testing more complex meniscus tears.

Joint (i.e., intra-articular) steroid injections are a standard treatment for OA pain, but their sustained clinical benefit is controversial. To address the long-term effects of this treatment, NIH-funded investigators examined 140 patients who were symptomatic for OA in the knee and who received intra-articular injections of triamcinolone or saline once every 12 weeks for 2 years.[1250] Their findings neither prove nor negate the effectiveness of intra-articular steroid injections for short-term relief of pain, and they also found no long-term effect on knee pain. In fact, the group that received the steroid showed signs of more extensive cartilage loss than the control group, suggesting that long-term use may result in adverse effects on preservation of knee cartilage.

Running and other high-impact exercises have been thought to be detrimental to knee joints and, consequentially, make knee OA worse. New data from the Osteoarthritis Initiative, a public–private partnership that NIH began in 2001, have shown that running is not associated with worsening of knee pain, nor with changes to the knee structure.[1251] Additionally, knee pain was more likely to improve over 48 months in runners than in non-runners. These results suggest that running is safe and beneficial to people with knee OA.

Older patients with knee osteoarthritis and other chronic medical conditions, such as heart disease and diabetes, often are prescribed acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or opioids to manage pain. To better understand which pain relief options are best for older patients with knee osteoarthritis, NIAMS-supported researchers examined the long-term clinical outcomes and economic costs associated with these common treatments. The study identified that the use of opioids provided

[1248] Quattrocelli M, et al. *J Clin Invest* 2017;127(6):2418-32. PMID: 28481224.
[1249] Tarafder S, et al. *Sci Rep* 2018;8(1):8150. PMID: 29802356.
[1250] McAlindon TE, et al. *JAMA* 2017;317(19):1967-75. PMID: 28510679.
[1251] Lo GH, et al. *Clin Rheumatol* 2018;37(9):2497-2504. PMID: 29728929.

less benefit than the use of the NSAID naproxen.[1252] This finding will help doctors prioritize treatment choices with their patients.

Osteoradionecrosis occurs due to lack of blood flow to the bone, which is a common side effect of radiation treatment for head and neck cancers. NIDCR-supported scientists demonstrated that imaging patients' jaws during radiation treatment could detect differences in the flow of blood to bone that correlated with the levels of radiation being delivered.[1253] Future clinical studies will examine if these changes result in increased risk of osteoradionecrosis.

NIAMS supports efforts with the HHS Office of Disease Prevention and Health Promotion and CDC for the completion of the Healthy People 2020 initiative and preparations for the implementation of Healthy People 2030.[1254] In FY 2016–2018, NIAMS continued as scientific leads in the Arthritis, Osteoporosis and Chronic Back Condition topic area and supported data collection to address the osteoporosis objectives to reduce the proportion of adults with osteoporosis and to reduce hip fractures among adults aged 65 years and older. The data collected through Healthy People over the years have been pivotal in understanding the natural history of the prevalence and incidence of arthritis and osteoporosis and establishing a baseline for future Healthy People 2030 objectives.

In FY 2017, NIA, NIAMS, and the NIH Office of Disease Prevention's Pathways to Prevention Program began developing an FY 2019 workshop to clarify major questions related to the safe, long-term use of bone-building or bone-preserving drugs and to identify evidence gaps and areas of future research.[1255] Drugs like bisphosphonates prevent fractures in older people who have osteoporosis. However, many people are reluctant to use them because of concerns about rare, but serious, side effects. Some experts consider the increase in underdiagnosis and undertreatment of osteoporosis to be the harbinger of a public health crisis.

NIAMS—in collaboration with NIA, NIDDK, and the NIH ORWH—leads the NIH Osteoporosis and Related Bone Diseases National Resource Center, which provides patients, health professionals, health educators, and the public with an important link to resources and information on metabolic bone diseases, including osteoporosis, Paget's disease of bone, and osteogenesis imperfecta.[1256] The center is dedicated to increasing the awareness, knowledge, and understanding of health professionals, patients, health educators, underserved and at-risk populations (e.g., Hispanic/Latino and Asian women, adolescents, and men), and the general public about the prevention, early detection, and treatment of osteoporosis and related bone diseases.

[1252] Katz JN, et al. *Osteoarthritis Cartilage* 2016;24(3):409-18. PMID: 26525846.
[1253] Joint Head and Neck Radiotherapy-MRI Development Cooperative. *Sci Rep* 2016;6:29864. PMID: 27499209.
[1254] https://www.healthypeople.gov/2020/topics-objectives/topic/Arthritis-Osteoporosis-and-Chronic-Back-Conditions/objectives.
[1255] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/appropriate-use-drug-therapies-osteoporotic-fracture-prevention.
[1256] https://bones.nih.gov/.

Obesity

More than one-third of U.S. adults (39.8 percent, or about 93.3 million people) are obese,[1257] and around 18.5 percent of children and adolescents suffer from obesity,[1258] making it one of the most common and complicated chronic diseases afflicting Americans. Childhood obesity puts children at risk for future health problems, and obesity-related problems among adults include dangerous health issues, such as heart disease, stroke, type 2 diabetes, and some forms of cancer. Furthermore, obesity is estimated to cost the U.S. more than $147 billion in annual medical spending.[1259] Because of obesity's prevalence, the number of complications related to obesity, and the high social and personal costs, NIH conducts a broad range of research activities to understand how and why people become obese, how to prevent and treat obesity, and how to unlock the basic biological activities behind obesity and its numerous complications.

Understanding Prevalence, Risk Factors, and Underlying Biology

Recent research by NIDDK-funded scientists has shed light on the brain's role in appetite and obesity. In one study, scientists discovered a mechanism by which antenna-like sensory projections, called primary cilia, located on brain cells play a role in the genetic predisposition to and development of obesity. Results from experiments in mice suggest that disruption of proteins located on primary cilia leads to dysregulation of appetite, providing new insights into the brain's influence over body weight and potentially opening the door to new approaches to treating and preventing obesity.[1260] In another study, researchers identified a group of brain cells, called ZI-GABA cells, that, upon activation, induces rapid binge eating and weight gain in mice, a finding that could lead to the development of novel treatment strategies for binge-eating disorders in humans.[1261]

Using disease in a dish technology, scientists supported by NCATS have recreated brain neurons of obese patients, offering a new method to study the brain's role in obesity and possibly tailor treatments to specific individuals.[1262,1263]

[1257] https://www.cdc.gov/obesity/data/adult.html.
[1258] https://www.cdc.gov/obesity/data/childhood.html.
[1259] https://www.cdc.gov/obesity/data/adult.html.
[1260] Siljee JE, et al. *Nat Genet* 2018;50(2):180-5. PMID: 29311635.
[1261] Zhang X and van den Pol AN. *Science* 2017;356(6340):853-9. PMID: 28546212.
[1262] https://www.cedars-sinai.org/newsroom/scientists-re-create-brain-neurons-to-study-obesity-and-personalize-treatment/.
[1263] Rajamani U, et al. *Cell Stem Cell* 2018;22(5):698-712.e9. PMID: 29681516.

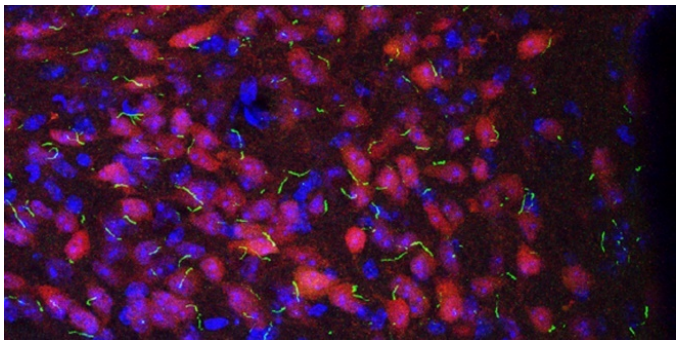

Figure 74. This image shows mouse neurons (purple) with their nuclei (blue) and primary cilia (green). Credit: Yi Wang, Vaisse Laboratory, University of California, San Francisco.

In the largest study of its kind to date, NIDDK-supported researchers used imaging technology to show that certain DNA sequence variants in a gene called *FTO* (fat mass and obesity–associated) raise obesity risk in humans by disrupting brain processing, leading to a weakened sense of fullness and subsequent overeating.[1264] The researchers found that when a group of participants with a high-risk variant were presented with images of fattening foods both before and after a meal, they experienced greater activation in certain brain regions that have known roles in food reward and food motivation; this activation was directly linked to greater food intake. Additional studies could provide greater insight into the role of FTO genetics in brain processing and obesity. Another research group supported by NHLBI found that people with certain *FTO* variants are at high risk for obesity. A meta-analysis of 10 weight loss trials suggests that among overweight adults, those with an *FTO* risk genotype may also lose more weight through diet and lifestyle interventions than those without this genotype.[1265] The results of the analysis provide evidence for the role of genetic variability in response to lifestyle interventions for weight loss and might help tailor such interventions to the people most likely to benefit.

In a controlled study of weight gain and loss, NIDDK-funded researchers have assembled a comprehensive molecular profile of dramatic changes that occur in humans during short periods of weight fluctuation. By using a variety of different analytical methods on a large scale, they collected more than 2 million measurements in both men and women and found that even short periods of weight gain affect metabolism, the microbiome, and heart health.[1266] Most of the changes, but not all, returned to normal upon subsequent weight loss. This research also highlighted the fact that individuals are unique at the molecular level, and further studies with the publicly available data generated by this study could lead to personalized, predictive molecular signatures for type 2 diabetes and other weight-related conditions long before a disease manifests.

An international research team led by an NHGRI intramural investigator has conducted the first study of its kind to look at the genomic underpinnings of obesity in continental Africans and African Americans.[1267]

[1264] Melhorn SJ, et al. *Am J Clin Nutr* 2018;107(2):145-54. PMID: 29529147.
[1265] Xiang L, et al. *Am J Clin Nutr* 2016;103(4):1162-70. PMID: 26888713.
[1266] Piening BD, et al. *Cell Syst* 2018;6(2):157-170.e8. PMID: 29361466.
[1267] https://www.genome.gov/news/news-release/Study-identifies-African-specific-genomic-variant-associated-with-obesity.

They discovered that approximately 1 percent of West Africans, African Americans, and others of African ancestry carry a genomic variant in the gene *SEMA4D* that increases their risk of obesity, a finding that provides insight into why obesity clusters in families. Individuals with this variant are about 6 pounds heavier on average than those without it.[1268]

NHLBI-funded researchers found that about 6 percent of approximately 8,500 participants in the Atherosclerosis Risk in Communities study carry a mutation in the *SGLT-1* gene that impairs glucose uptake in the intestine.[1269] Individuals with this mutation had a lower incidence of heart failure and type 2 diabetes, had a lower mortality rate, and were less obese, even after adjusting for dietary intake. Thus, selectively blocking the SGLT-1 receptor in the intestine could provide a way to slow down glucose uptake to prevent or treat diabetes and reduce the risk of obesity and heart disease.

In October 2018, OBSSR supported a special issue in the journal *Childhood Obesity* that included six articles reporting the findings from the National Collaborative on Childhood Obesity Research Childhood Obesity Declines Project.[1270] This project aims to improve understanding of possible drivers and contributors that may be influencing the decline in the rates of childhood obesity in some groups or regions and to explore how these may be related to other health promotion efforts.[1271] OBSSR also supported another special issue, in *Obesity*, following a meeting of multidisciplinary biobehavioral scientists and NIH program staff, to highlight mechanisms associated with humans' ability to self-regulate appetite and appetitive behavior.[1272]

NIEHS research showed that young women with high body fat have a decreased chance of developing breast cancer before menopause. The scientists determined that relative risk of premenopausal breast cancer was reduced 12–23 percent for each five-unit increase in BMI, depending on age.[1273] The strongest effect was seen in relation to BMI at ages 18–24 years, with very obese women in this age group being 4.2 times less likely to develop premenopausal breast cancer, compared with women with low BMI at the same age.

Both obesity and the use of hormonal oral contraceptives are independent risk factors for venous thromboembolism. Researchers in NICHD's Contraceptive Clinical Trials Network are testing contraceptive methods that act on progesterone receptor modulators.[1274] This could provide a contraceptive regimen that is easier to follow and has a lower risk of venous thromboembolism, especially for women with obesity. Researchers will conduct a sequence of studies, ultimately including an RCT, to evaluate the pharmacokinetic and pharmacodynamic profile, contraceptive efficacy, bleeding patterns, safety, side effects, and acceptability of these contraceptive agents in women with and without obesity. In 2017, pilot testing showed that an injectable form of the contraceptive inhibited ovulation, but the return to

[1268] Chen G, et al. *Obesity.* 2017;25(4):794-800. PMID: 28296344.
[1269] Seidelmann SB, et al. *J Am Coll Cardiol* 2018;72(15):1763-73. PMID: 30286918.
[1270] Young-Hyman D, et al. *Child Obes* 2018;14(S1):S40-S44. PMID: 29565656.
[1271] https://www.nccor.org/projects/obesity-declines/.
[1272] Young-Hyman D. *Obesity* 2017;25 Suppl 1:S5-S7. PMID: 28229540.
[1273] Premenopausal Breast Cancer Collaborative Group, et al. *JAMA Oncol* 2018;4(11):e181771. PMID: 29931120.
[1274] https://www.nichd.nih.gov/research/supported/cctn.

ovulation was earlier than had been expected and was earlier in women with obesity, compared with women with no obesity. Research to develop a preparation suitable for a longer-lasting product is ongoing.

Chronic obstructive pulmonary disease (COPD) is currently the fifth-leading cause of death worldwide; the majority of cases are caused by environmental factors, such as tobacco smoke. Both body mass and obesity have also been associated with worse COPD outcomes. Researchers supported by NIEHS wanted to understand whether obese individuals with moderate-to-severe COPD were more susceptible to the adverse effects of particulate matter on respiratory morbidity than non-obese individuals. They measured exposure to particulate matter with $PM_{2.5}$ among 84 former smokers with moderate-to-severe COPD, 56 percent of whom were obese (BMI greater than 30 kg/m^2). The study results indicated that obesity modified the effects of indoor particulate matter on COPD respiratory outcomes, with obese patients exhibiting exaggerated exacerbations related to particulate matter exposure, such as wheeze and airway and systemic inflammatory responses.[1275]

Investigators from the National Toxicology Program and EPA are collaborating on a project to screen approximately 70 chemicals for their ability to induce the differentiation of fat cells (adipocytes) and lipid production in a cell model. These potential obesogens were chosen for their ability to activate specific targets within the Tox21 assays.[1276] Novel results from these screens are generating additional investigations on such chemicals as pyrethroid pesticides, parabens, and bisphenols that may be replacements for BPA. A recent publication reports that numerous early genes are responsible for adipogenic and lipogenic events occurring in this cell model following tetrabromobisphenol A exposure. Tetrabromobisphenol A is the most common flame retardant used in electrical housings. The early genes prohibiting differentiation into an adipocyte are downregulated, and numerous early genes in the nontraditional estradiol receptor and glucocorticoid receptor pathways are upregulated, leading to an increased number of mature adipocytes and more lipid accumulation.

Research on calorie-burning brown and beige fat tissue is opening potential new avenues for obesity treatment. For example, through experiments in mouse cell lines, male mice, and human tissue samples, NIDDK-supported scientists have identified the molecule NF1A as critical to activation and development of brown fat, a finding that may lead to new therapies, potentially through development of ways to manipulate NF1A to reprogram cells to become brown fat.[1277] In another study, NIDDK-funded scientists developed a novel technique in mice for directing stem cells from body fat to grow in special gels and form brown fat.[1278] Future studies could test this technology in human cells, potentially making it possible for a person's own body fat to be used for generating calorie-burning cells.

Improving Treatment and Prevention

[1275] McCormack MC, et al. *Eur Respir J* 2015;45(5):1248-57. PMID: 25573407.
[1276] https://ntp.niehs.nih.gov/whatwestudy/tox21/index.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tox21.
[1277] Hiraike Y, et al. *Nat Cell Biol* 2017;19(9):1081-92. PMID: 28812581.
[1278] Tharp KM, et al. *Diabetes* 2015;64(11):3713-24. PMID: 26293504.

The Intervention Nurses Start Infants Growing on Healthy Trajectories (INSIGHT) study supported by NIDDK was a randomized trial that examined the effects of a responsive parenting intervention designed for obesity prevention in infants.[1279] The study found that responsive parenting in feeding can prevent the use of food to soothe and promote structure-based feeding, which could reduce obesity risk by affecting how and when infants are fed in the first year of life.[1280] The responsive parenting intervention was associated with reduced rapid weight gain during the first 6 months after birth and overweight status at 1 year of age, as well as improvement in body weight (as measured by BMI z-scores) of the children, compared with a control group, through 3 years old.[1281,1282] A long-term follow-up study will evaluate the children through age 9 years.

Sedentary children have greater risk of obesity and may experience abnormalities in how they process glucose (sugar), even before they develop diabetes or prediabetes. NICHD-supported researchers found that interrupting sedentary behavior (sitting) with very short periods of walking improved glucose metabolism, without affecting food intake, in children who had overweight or obesity.[1283] Children aged 7–11 years with overweight or obesity underwent two experiments in random order: (1) prolonged sitting (3 hours of continuous sitting) and (2) interrupted sitting (sitting interrupted every 30 minutes with 3 minutes of moderate-intensity walking, over a total time of 3 hours). The researchers measured biomarkers for how the children metabolized glucose, as well as the children's food intake at a buffet meal after each session. Interrupting sedentary behavior, even with short walking sessions, may be a promising intervention strategy for reducing health risks in overweight children.

An NIH Common Fund–supported Early Independence Awardee is investigating how children and adolescents are exposed to unhealthy food and beverages. As reported in a 2016 paper, the researcher found that music celebrities popular among adolescents overwhelmingly endorsed unhealthy food and beverages.[1284] In a 2018 paper, the researcher reported that the top 10 most-watched sports organizations among children aged 2–17 years primarily advertised food products that are rated unhealthy by a respected nutritional value food-rating system.[1285] These research studies raise concerns that advertising and endorsements could have a negative impact on children's food choices.

Although childhood obesity is common in the U.S., the dosage for many medications used in children is based on factors other than body weight, which may result in children who have overweight or obesity receiving less medicine than they need. Clindamycin is an antibiotic that is frequently used in children for serious infections. Researchers combined data from several studies to assess how clindamycin is absorbed, metabolized, and cleared by the body in children with and without obesity.[1286] The results

[1279] https://www.clinicaltrials.gov/ct2/show/NCT01167270?term=NCT01167270&rank=1.
[1280] Savage JS, et al. *JAMA Pediatr* 2016;170(8):742-9. PMID: 27271455.
[1281] Savage JS, et al. *Int J Behav Nutr Phys Act* 2018;15(1):64. PMID: 29986721.
[1282] Paul IM, et al. *JAMA* 2018;320(5):461-8. PMID: 30088009.
[1283] Broadney MM, et al. *Diabetes Care* 2018;41(10):2220-8. PMID: 30082324.
[1284] Bragg MA, et al. *Pediatrics* 2016;138(1). pii: e20153977. PMID: 27273712.
[1285] Bragg MA, et al. *Pediatrics* 2018;141(4). pii: e20172822. PMID: 29581181.
[1286] Smith MJ, et al. *Antimicrob Agents Chemother* 2017;61(4). PMID: 28137820.

indicated that dosing by total body weight could help ensure that clindamycin is safe and effective for both obese and non-obese children.

Building on promising results of a preliminary trial, NICHD-supported investigators will conduct a larger, longer-term controlled trial of an intervention intended to help adolescents with intellectual and developmental disability lose weight.[1287] The intervention, which will enroll both adolescents and their supporting parents/caregivers, includes portion-control diets (self-reported on paper or electronically through commercial programs) and progressive increase in exercise. Delivery of the intervention will be via in-home visits or electronic communication.

NIDDK has supported the Teen-LABS (Longitudinal Assessment of Bariatric Surgery) observational study to assess the short- and long-term risks and benefits of bariatric surgery among teens with severe obesity and serious weight-related health problems who were already planning to have the surgery.[1288,1289] Three years after weight-loss surgery, researchers found major improvements in weight, heart health, and other measures. Participants lost approximately 90 pounds on average, or 27 percent of their weight, and most of the teens who had type 2 diabetes, prediabetes, high blood pressure, abnormal kidney function, and high blood cholesterol when the study began showed improvements in these conditions after the surgery.[1290] In 2016, NIDDK extended funding for Teen-LABS for several more years to allow the researchers to gain additional information from participants on longer-term benefits and risks of the surgery.

An intervention study showed that overweight or obese women who carry a common variant of the *CLOCK* (circadian locomotor output cycles kaput) circadian gene, which makes them more susceptible to obesity, lost 36 percent less weight after 20 weeks on a Mediterranean-based diet compared with non-carriers.[1291] The variant also was associated with later wake-up and meal times and reduced variability in daily heart rate. These findings point to potential application of circadian-based molecular and physiological markers to predict individual differences in response to weight loss interventions.

Researchers found that a prenatal behavioral intervention with partial meal replacement significantly reduced gestational weight gain in Hispanic and non-Hispanic women with overweight and obesity.[1292] Partial meal replacement consisted of replacing two meals per day with provided shakes or bars while also consuming at least one meal of regular foods and two to four healthy snacks.

NIDDK has supported multiple studies to gain insight into ways to achieve healthy weight gain during pregnancy. For example, the Lifestyle Interventions for Overweight and Obese Pregnant Women (LIFE-Moms) consortium's clinical trials, supported by NIDDK in collaboration with other NIH ICs, found that the

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[1287] https://projectreporter.nih.gov/project_info_description.cfm?aid=9450525&icde=43408312.
[1288] https://www.clinicaltrials.gov/ct2/show/NCT00474318.
[1289] https://www.niddk.nih.gov/about-niddk/research-areas/obesity/bariatric-surgery-teens-severe-obesity-study-teen-labs.
[1290] Inge TH, et al. *N Engl J Med* 2016;374(2):113-23. PMID: 26544725.
[1291] Lo MT, et al. *Int J Obes* 2018;42(2):190-7. PMID: 28736443.
[1292] Phelan S, et al. *Am J Clin Nutr* 2018;107(2):183-94. PMID: 29529157.

interventions reduced excess gestational weight gain, showing that gestational weight management is possible with lifestyle interventions in diverse populations.[1293] However, no effects on other maternal or infant outcomes were seen, and it is unclear if the modest differences in gestational weight gain are enough to have future health benefits in mothers or their offspring, highlighting the importance of further research in this area. Other NIDDK-funded studies are shedding light on calorie consumption and calorie burning during pregnancy in women of varying racial and ethnic backgrounds with obesity, which could inform development of new, personalized strategies to promote healthy gestational weight gain and reduce racial disparities in pregnancy outcomes.[1294,1295]

The outcomes of bariatric surgery for the treatment of obesity may have variable success if patients are exposed to high levels of environmental pollutants. NIEHS-funded researchers found that exposures to $PM_{2.5}$ and nitrogen dioxide were associated with reduced weight loss and metabolic benefits of laparoscopic adjustable gastric banding.[1296] These findings point to a potential model for studying metabolic effects of environmental exposures.

Investigators studied 30 obese women with an average age of 48.2 years to address whether changes in glucose metabolism and fat depots following bariatric surgery affect bone. They examined changes in bone marrow fat, which is a dynamic and unique fat depot thought to regulate both bone and fat. Data from diabetic and nondiabetic women suggest that glucose metabolism and weight loss may influence marrow fat, which, in turn, seems to influence bone mineral density.[1297] Ultimately, understanding the role of marrow fat in bone metabolism could facilitate developing strategies that target the skeletal complications of bariatric surgery, diabetic bone fragility, and the prevention and treatment of osteoporosis, in general.

Led by NIDDK in collaboration with other NIH ICs, Action for Health in Diabetes (LookAHEAD) was an RCT comparing the effects of intensive lifestyle intervention focused on weight loss achieved through healthy eating and increased physical activity, compared to a control condition of diabetes support and education, in people with overweight or obesity and type 2 diabetes.[1298] The Look AHEAD Extension will examine whether intensive lifestyle intervention, provided for 10 years during midlife, has enduring benefits (increased lifespan, reduced health care costs, healthy aging) that persist beyond the intervention period for older individuals with obesity and type 2 diabetes.

The year 2017 marked the 20th anniversary of the publication that reported the blood pressure–lowering effects of NHLBI's Dietary Approaches to Stop Hypertension (DASH) intervention.[1299] The DASH diet is considered an important advance in nutritional science. The diet emphasizes foods rich in protein, fiber, potassium, magnesium, and calcium, such as fruits and vegetables, beans, nuts, whole grains, and low-fat

[1293] Peaceman AM, et al. *Obesity* 2018;26(9):1396-404. PMID: 30230252.
[1294] Most J, et al. *Obesity* 2018;26(6):992-9. PMID: 29797559.
[1295] Most J, et al. *Am J Clin Nutr* 2018;107(6):957-64. PMID: 29767680.
[1296] Ghosh R, et al. *Pediatr Obes* 2018;13(5):312-20. PMID: 28429404.
[1297] Kim TY, et al. *J Bone Miner Res* 2017;32(11):2239-47. PMID: 28791737.
[1298] https://clinicaltrials.gov/ct2/show/NCT00017953.
[1299] https://www.nhlbi.nih.gov/news/2017/dash-diet-20-years-later.

dairy. The diet also limits foods high in saturated fat and sugar. Numerous trials have demonstrated that the DASH diet consistently lowers blood pressure across a diverse range of patients with hypertension and prehypertension.[1300]

The Healthy Communities Study funded by NHLBI found that communities with comprehensive programs and policies that promote a greater amount, type, and duration of exercise and nutrition behaviors were associated with lower average childhood BMI, compared with communities without comprehensive programs and policies.[1301] Relationships between comprehensive programs and policies and BMI differed significantly by a child's grade in school, race and ethnicity, family income, parental education, and community-level race and ethnicity.

Pulmonary Diseases

Many different types of pulmonary diseases affect the lungs and respiratory system. COPD, for example, has been diagnosed in more than 16 million Americans.[1302] Another common pulmonary disorder is sleep apnea, in which a person has one or more pauses in breathing or shallow breaths while sleeping. Around 25 million Americans suffer from sleep apnea,[1303] which can increase a person's risk for heart failure, stroke, obesity, diabetes, and high blood pressure.[1304] NIH's research on pulmonary diseases seeks to disentangle the complex biological underpinnings of these and other conditions, understand who is afflicted by them and why, and treat and prevent their occurrence.

Figure 75. "Common Signs of COPD": Infographic. Credit: NHLBI.

Understanding Prevalence, Risk Factors, and Underlying Biology

NHLBI, along with federal and nonfederal partners, released the first-ever COPD National Action Plan in May 2017.[1305] The plan is a detailed, patient-centered roadmap for addressing one of the most urgent

[1300] Steinberg D, et al. *JAMA* 2017;317(15):1529-30. PMID: 28278326.
[1301] Frongillo EA, et al. *Am J Prev Med* 2017;53(5):576-83. PMID: 28688728.
[1302] https://www.cdc.gov/copd/index.html.
[1303] https://aasm.org/rising-prevalence-of-sleep-apnea-in-u-s-threatens-public-health/.
[1304] https://www.nhlbi.nih.gov/health/health-topics/topics/sleepapnea.
[1305] https://www.nhlbi.nih.gov/health-topics/education-and-awareness/COPD-national-action-plan.

health concerns facing Americans. Although COPD is not curable, it is often preventable and highly treatable, and early diagnosis can lead to improved outcomes. The newly released action plan, developed with input from the broad COPD community, builds on what the health and scientific communities already know about the disease. The action plan focuses on five goals, including raising public awareness of COPD risk factors; increasing research to better understand, prevent, and treat the disease; and translating findings into public health action.

New data from an ongoing collaboration between NHLBI and CDC show that COPD is almost twice as common in rural areas as in urban settings. To address this disparity, the NHLBI initiated new efforts with CDC, HRSA, and Federal Office of Rural Health Policy. NHLBI and its partners convened two workshops on COPD and rural health in 2018.[1306] These workshops addressed how to better meet the challenges of diagnosing and treating COPD in rural America, such as through telemedicine.

NHLBI-funded researchers found a heritable pattern of airway branching that is common in people with COPD; they also found a heritable pattern that is common in smokers with COPD.[1307] These patterns included increased and narrower branches, changes that may make it easier for pollutants to accumulate in the airway and cause damage. This finding is significant because branch patterns, which can be easily imaged using CT scans, could be used as a biomarker for COPD susceptibility.[1308]

To explore research needs and opportunities related to the impact of female sex and gender on lung health and management of lung disease, NHLBI collaborated with ORWH and the Office of Rare Diseases Research to hold a September 2017 workshop titled *"Female Sex and Gender in Lung/Sleep Health and Disease: Increased Understanding of Basic Biological, Pathophysiological and Behavioral Mechanisms Leading to Better Health for Female Patients with Lung Disease."* NIH staff and investigators studying sleep disorders and lung diseases, including COPD and pulmonary hypertension, discussed the current understanding of sex differences influencing these conditions, future research priorities, and potential areas of collaboration.[1309]

Approximately 8,500 women with HIV give birth annually in the U.S. Previous research indicated that youths who were exposed to and infected with HIV in the womb have an increased risk for asthma, compared with youths who were exposed to HIV in the womb but uninfected. NICHD-supported researchers reviewed medical records and reports for 218 youths with HIV and asthma and 152 young people with asthma who had been exposed to HIV before birth but were uninfected.[1310] The researchers administered pulmonary function tests to these youths to classify the types of lung disease. To distinguish asthma from other causes of obstructive lung disease, a reversibility test is used to measure the flow of air into the lungs before and after treatment; in asthma, treatment can usually reverse the obstruction of airflow. In this study, the prevalence of obstructive lung disease did not differ by HIV status, but obstruction of airflow was less likely to be reversible in the youths with HIV than in the uninfected youths.

[1306] https://www.nhlbi.nih.gov/events/2018/copd-rural-health-dialogue-national-action-plan.
[1307] Smith BM, et al. *Proc Natl Acad Sci USA* 2018;115(5):E974-81. PMID: 29339516.
[1308] https://www.nih.gov/news-events/news-releases/new-study-offers-insights-genetic-indicators-copd-risk.
[1309] Han MK, et al. *Am J Respir Crit Care Med* 2018;198(7):850-8. PMID: 29746147.
[1310] Shearer WT, et al. *J Allergy Clin Immunol* 2017;140(4):1101-11.e7. PMID: 28279683.

Youth with HIV also had lower levels of allergen-associated antibodies and lower ratios of different white blood cells, which indicate an immune imbalance. These findings indicate that youths with HIV may be more prone to a complex combination of asthma and COPD and should be further observed to determine lung disease outcomes in adulthood.

Using data from more than 220,000 electronic health records, NICHD intramural researchers assessed the possible role of prenatal air pollution exposure and/or maternal asthma in the risk of neonatal respiratory complications.[1311] The scientists found significant associations between neonatal respiratory complications and prenatal exposure to common air pollutants, including particulate matter, carbon monoxide, and nitrogen oxides. Although maternal asthma also increased risk, the researchers found that the relation with air pollution was separate from maternal asthma as an independent factor in the newborns' illnesses.

Pulmonary emphysema is a chronic inflammatory lung disease in which airflow becomes limited. Together with other forms of smoking-related COPD, pulmonary emphysema represents a leading cause of death in the U.S. NHLBI-funded researchers found that miRNAs—lesser known partner molecules of DNA—are key components of the molecular pathway leading to pulmonary emphysema. The investigators found that the miRNA known as miR-22 is increased in the lungs of smokers with emphysema and essential for the development of emphysema in mice exposed to cigarette smoke.[1312] Because mice deficient in miR-22 did not develop emphysema, selective inhibition of miR-22 could be an effective therapy for emphysema and other inflammatory diseases.[1313]

NHLBI's Subpopulations and Intermediate Outcome Measures in COPD (SPIROMICS) study is looking at genetic, clinical, biological, and other data, including lung imaging, to help understand risk factors for COPD and poor outcomes from the disease.[1314] In a finding that could lead to better treatment of smoking-related lung diseases, SPIROMICS researchers report that about half of current or former smokers have respiratory symptoms similar to COPD and an increased risk for exacerbations or flare-ups of their symptoms, despite normal lung function and a lack of COPD diagnosis.[1315] Using CT imaging scans of the lung, the researchers also found a high incidence of thickening of the airways, a sign of lung disease.[1316]

The COPDGene Study is one of the largest studies ever to investigate the underlying genetic factors for COPD. COPDGene is a cross-sectional prospective cohort study that enrolled participants between January 2008 and June 2011 at 21 clinical centers. In 2018, researchers analyzed lung imaging, genomic, and clinical data from nearly 15,000 people and found a gene variant that improved risk prediction for fibrotic lung disease when added to a risk algorithm that included age, sex, and smoking status.[1317]

[1311] Seeni I, et al. *Ann Epidemiol* 2018;28(9):612-18.e4. PMID: 30153910.
[1312] Lu W, et al. *Nat Immunol* 2015;16(11):1185-94. PMID: 26437241.
[1313] https://www.nhlbi.nih.gov/news/2016/select-2015-nhlbi-science-advances.
[1314] https://www.spiromics.org/spiromics/.
[1315] https://www.nhlbi.nih.gov/news/2016/study-finds-copd-respiratory-symptoms-common-among-smokers-despite-lack-copd-diagnosis.
[1316] Woodruff PG, et al. *N Engl J Med* 2016;374(19):1811-21. PMID: 27168432.
[1317] Putman RK, et al. *Eur Respir J* 2017;50(3). PMID: 28893869.

Another genetic study looked at people with and without COPD and found 22 potential genes associated with the disease.[1318] Several of the genes were previously known to be involved in lung function. Additionally, the study found shared genetic risk factors between COPD and pulmonary fibrosis—a disease in which tissue deep in the lungs becomes thick and stiff, or scarred, over time.

An NHLBI-funded study examined the role of the immune system in pulmonary fibrosis and found an increase in levels of a protein called programmed cell death-1 (PD-1) in helper T-cells, the white blood cells that regulate the body's response to infection.[1319] Blocking PD-1 and a related signaling pathway reduced signs of fibrosis in a mouse model of pulmonary fibrosis, suggesting that this pathway could be targeted effectively by drugs that are already FDA-approved for other conditions.

Interstitial lung disease is the leading cause of death in patients who have a type of scleroderma called systemic sclerosis (SSc). Interstitial lung disease has an unpredictable trajectory, especially for people who are in the early stages of SSc. To determine whether any changes in a patient's blood could predict the development of this complication, a group of researchers examined samples and data collected through two studies of scleroderma patients—the Genetics versus Environment in Scleroderma Outcome Study and the Canadian Scleroderma Research Group.[1320] Analysis of both groups independently revealed an association between higher blood levels of the chemokine C-C motif ligand 2, also known as CCL2, and faster declines in lung function, suggesting that CCL2 can be used to identify patients who are at highest risk of rapidly progressing interstitial lung disease.[1321] The findings also support earlier work that indicates CCL2 could be a potential target for SSc therapies.

NIH researchers have demonstrated that mice deficient in a protein called iron-responsive element-binding protein 2 were protected from cigarette smoke–induced experimental COPD.[1322] During the study, mice treated with a mitochondrial iron chelator or mice fed a low-iron diet were protected from cigarette smoke–induced COPD. Mitochondrial iron chelation also alleviated cigarette smoke–induced pulmonary inflammation and cigarette smoke–associated lung injury in mice with established COPD, suggesting a critical functional role and potential therapeutic intervention, such as mitochondrial iron chelators, for COPD.

NIEHS intramural researchers conducted an epigenome-wide association study of COPD and lung function in Koreans. They found evidence of an association between one site and 104 regions.[1323] Using gene expression data from another Korean cohort, the authors found that for 34 of the genes in these regions, expression was related to the same trait that was found to be differentially modified or methylated.

[1318] Hobbs BD, et al. *Nat Genet* 2017 Mar;49(3):426-32. PMID: 28166215.
[1319] Celada LJ, et al. *Sci Transl Med* 2018;10(460). pii: eaar8356. PMID: 30257954.
[1320] https://www.niams.nih.gov/newsroom/spotlight-on-research/researchers-identify-potential-biomarker-serious-scleroderma.
[1321] Wu M, et al. *Arthritis Rheumatol* 2017;69(9):1871-8. PMID: 28575534.
[1322] Cloonan SM, et al. *Nat Med* 2016;22(2):163-74. PMID: 26752519.
[1323] Lee MK, et al. *Epigenomics* 2017;9(7):971-84. PMID: 28621160.

Pathway analyses highlighted fundamental developmental pathways. It is possible that DNA methylation could contribute to the pathogenesis of reduced lung function and COPD.

NIEHS grantees have uncovered the key molecular pathway involved in COPD induced by air pollution exposure. Although cigarette smoke is the most common irritant that causes COPD, at least one-fourth of people with COPD are nonsmokers and thus could have COPD linked to air pollution.[1324]

Indoor air pollution from smoky, inefficient cookstoves affects nearly 3 billion people, mostly in poorer countries, and contributes to an estimated 3.5 million deaths each year. Unsafe stoves can cause severe pneumonia in children and cardiovascular disease, COPD, and lung cancer in adults. Researchers analyzed data from more than 650 urban and rural households in Malawi, a country with a rapidly growing population and where indoor air pollution is a major public health concern.[1325] The scientists found that women in rural households had higher rates of many symptoms associated with indoor air pollution. Use of low-quality firewood and crop residues were associated with a variety of symptoms, including shortness of breath, difficulty breathing, and chest pains. However, the associations among types of fuels, rural versus urban location, and health outcomes were mixed. The results suggest that although long-term strategies are needed to reduce indoor air pollution, encouraging sustainable use of higher quality biomass fuels could have beneficial health effects in the short term.

Opportunistic tuberculosis infection is a common comorbidity with HIV, resulting in a dual epidemic, and a cause of significant mortality. Chest X-ray screening is commonly used to detect pulmonary tuberculosis and other cardiopulmonary abnormalities, such as cardiomegaly, pneumothorax, and opacity.[1326] Although chest X-ray screening is an effective low-cost approach to improve diagnosis and management, it is difficult to carry out in resource-poor countries with high disease burden and where radiological expertise is scarce. NLM is supporting a project to develop image-analysis and machine-learning algorithms to process chest X-rays, with the ultimate goal of implementing field-deployable systems to automate chest X-ray screening.[1327] This research has resulted in novel image-analysis algorithms (graph cut, atlas based) that identify lung boundaries and delineate lung regions in the posteroanterior chest X-rays.[1328–1331] The research has also resulted in novel combinations of shape, edge, and texture descriptors computed from pixels within the lung boundaries.[1332,1333] These image descriptors are then used to train supervised machine-learning classifiers (e.g., convolutional neural network–based deep learning). NLM also conducted deep-learning research on detecting and classifying pneumonia in pediatric chest X-rays from children aged 1 to 5 years. The result was a highly accurate pneumonia detection

[1324] Li X, et al. *Proc Natl Acad Sci USA* 2017;114(45):E9655-64. PMID: 29078374.
[1325] Das I, et al. *Ecohealth* 2017;14(1):7-19. PMID: 27800583.
[1326] Jaeger S, et al. *Int J Comput Assist Radiol Surg.* 2018;13(12):1915-25. PMID: 30284153.
[1327] Santosh KC and Antani S. *IEEE Trans Med Imaging* 2018;37(5):1168-77. PMID: 29727280.
[1328] Kallianos K, et al. *Clin Radiol* 2019;74(5):338-45. PMID: 30704666.
[1329] Rajaraman S., et al. *Conf Proc IEEE Eng Med Biol Soc* 2018;2018:718-21. PMID: 30440497.
[1330] Dhoot R, et al. *BMJ Glob Health* 2018;3(5):e000947. PMID: 30364326.
[1331] Vajda S, et al. *J Med Syst* 2018;42(8):146. PMID: 29959539.
[1332] Santosh KC, et al. *Int J Comput Assist Radiol Surg* 2016;11(9):1637-46. PMID: 26995600.
[1333] Candemir S, et al. *Comput Med Imaging Graph* 2016;51:32-9. PMID: 27156048.

algorithm that could aid in diagnosis and treatment by distinguishing between bacterial and viral pneumonia with 90 percent sensitivity and 96 percent specificity.

Alveoli, the air-filled sacs in the lungs, are made up two kinds of cells: alveolar type 1 (AT1) cells and alveolar type 2 (AT2) cells. AT1 cells line the alveoli and mediate gas exchange. AT2 cells have dual functions—they make surfactant and can turn into AT1 cells to help repair damaged alveoli. Two NHLBI-funded teams discovered that this transition depends on Wnt, a protein that stimulates AT2 cells to divide.[1334,1335] Lung injuries trigger AT2 cells themselves to make Wnt, dividing more rapidly to generate more AT2 cells, plus AT1 cells. The findings may lead to new regenerative medicine treatments for degenerative lung diseases and lung cancer.

Improving Treatment and Prevention

NCATS helped shepherd a potential new drug for a deadly lung disease (autoimmune pulmonary alveolar proteinosis, or aPAP) through many steps of the translational science process and provided a bridge that moved this therapeutic from preclinical to clinical research.[1336] First, academic and industry researchers collaborated with NCATS Therapeutics for Rare and Neglected Diseases (TRND) scientists on preclinical testing. CTSA program support enabled researchers to begin an early study of the experimental drug in patients. NCATS helped shepherd the potential therapy through several steps of the drug development process, ultimately enabling a clinical trial in the patients. The outlook continues to improve for an inhaled granulocyte/macrophage colony-stimulating factor therapy to become the first noninvasive treatment available for aPAP patients, with Phase I and Phase III trials underway.

Although Medicare began covering pulmonary rehabilitation in 2010, NHLBI-funded researchers have found that its use remains low.[1337] In 2012, of about 224,000 individuals hospitalized for COPD, only 1.9 percent received pulmonary rehabilitation within 6 months of their index hospitalization, and 2.7 percent did so within 12 months. A funding opportunity released in 2017 awarded several grants to support development of novel approaches to pulmonary rehabilitation, including home-based programs, computer-mediated patient counseling, and other messaging techniques to improve utilization.

Lung transplantation remains the only effective therapy for many patients with pulmonary fibrosis. In a large genetic study of idiopathic pulmonary fibrosis, researchers found that certain gene expression patterns in blood cells can predict a patient's response to therapy.[1338] This work could help guide the choice of treatment for pulmonary fibrosis, including identifying patients for whom lung transplant remains the best option.

Past research has shown that long-term oxygen treatment improves survival in those with COPD and severely low levels of blood oxygen. However, a long-standing question remains whether those with

[1334] Nabhan AN, et al. *Science* 2018;359(6380):1118-23. PMID: 29420258.
[1335] https://protocolexchange.researchsquare.com/article/nprot-6541/v1.
[1336] https://ncats.nih.gov/pubs/features/trnd-apap.
[1337] Spitzer KA, et al. *Ann Am Thorac Soc* 2019;16(1):99-106. PMID: 30417670.
[1338] Herazo-Maya JD, et al. *Lancet Respir Med* 2017;5(11):857-68. PMID: 28942086.

moderately low levels of blood oxygen also benefit. The Long-Term Oxygen Treatment Trial study was designed to answer this question.[1339] The study confirmed that, on average, supplemental oxygen is beneficial for severe COPD—but not for moderate cases—indicating a need for further research to improve outcomes for these patients.[1340]

NICHD-supported researchers used mice to study the link between gut bacteria and the immune system. The researchers fed pregnant mice antibiotics, which eliminated the gut bacteria of their offspring, and compared these newborn mice with newborn mice not exposed to antibiotics. The researchers confirmed that healthy gut bacteria were critical to preventing pneumonia in the newborn mice.[1341] They also discovered why: Bacteria in the gut signaled a type of immune system cell to move out of the gut and into the lung. These cells make a molecule called interleukin-22, which protects the lung from bacteria that cause disease. The researchers found that human infants whose mothers received antibiotics late in pregnancy also had less interleukin-22 in their lungs. The results help explain why antibiotic use during pregnancy and cesarean delivery, which disrupts transfer of healthy bacteria to the newborn gut, can increase the risk for infection in newborns.

NHLBI funded a randomized comparative effectiveness trial to determine whether intensive telephone counseling is an effective strategy for smoking cessation for patients with low resources, compared to standard quit-line methods. Participants in the study received either (1) seven telephone counseling sessions from Master's-level counselors with mental health training or (2) one 15- to 20-minute phone counseling session from their state's quit line, during which counselors who were trained in motivational interviewing focused on developing a plan to quit smoking.[1342] Intensive counseling was more effective, with excellent long-term abstinence.

NHLBI supports the COPD Learn More Breathe Better® program to increase awareness and understanding of COPD among patients, people at risk, loved ones, caregivers, and providers.[1343] In 2018, NHLBI expanded the program to support implementation of the COPD National Action Plan and awarded six contracts to state and local organizations to advance outreach and education through innovative community-level programs.[1344]

NHLBI leadership participated in the University of Minnesota Pulmonary Fibrosis Patient Education Day on May 13, 2017, and September 22, 2018. The events included sessions for patients with pulmonary fibrosis and their caregivers on research, clinical trials, new and existing treatments, and social support

[1339] https://www.nhlbi.nih.gov/news/2016/long-term-oxygen-treatment-trial-lott-frequently-asked-questions.
[1340] Long-Term Oxygen Treatment Trial Research Group, et al. *N Engl J Med* 2016;375(17):1617-27. PMID: 27783918.
[1341] Gray J, et al. *Sci Transl Med* 2017;9(376). PMID: 28179507.
[1342] Sherman SE, et al. *Am J Prev Med* 2016;51(4):566-77. PMID: 27647057.
[1343] https://www.nhlbi.nih.gov/health-topics/education-and-awareness/copd-learn-more-breathe-better/about-lmbb.
[1344] https://www.nhlbi.nih.gov/health-topics/education-and-awareness/copd-learn-more-breathe-better/community-subcontractor-program.

for the participants. NHLBI leaders discussed progress in funding basic and translational biomedical research that can be translated into new therapies for patients.

Substance Use and Addiction

Nearly four decades of research supported by NIH have shown substance addiction to be a complex brain disease characterized by compulsive—at times uncontrollable—drug craving, seeking, and use that persists despite potentially devastating consequences. Millions of Americans suffer from substance use disorder (SUD)—including, but not limited to, addiction—and with them, their families suffer as well.

In 2017, more than 70,000 people in the U.S. died of opioid overdose,[1345] and an estimated 88,000 die from alcohol-related causes each year.[1346] SUD and addiction affects Americans of every race, ethnicity, sex, gender, age group, and socioeconomic class. Improvements in understanding, prevention, and treatment of SUDs, including opioid use disorder (OUD) and fetal alcohol spectrum disorder (FASD), require a research portfolio that explores the complex factors that contribute to it. NIH, led by NIAAA and NIDA, invests in areas relevant to understanding SUDs, including addiction research and biological, clinical, social, and epidemiological factors of substance use.

Crosscutting, Trans-NIH Efforts

Although NIH investments span SUDs across many substances, a series of high-priority areas exist for NIH. Collaboration across NIH and with other federal agencies in these areas is an important strategy critical to making progress.

Helping to End Addiction Long-term Initiative and other Trans-NIH Activities to Address the Opioid Epidemic

One of these areas of coordination is in addressing the epidemic of opioid use within the U.S. More than 2 million Americans have disorders stemming from opioid use and misuse, and 50 million more suffer from daily chronic pain. In April 2018, NIH launched a national, trans-agency research effort called the Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠. Undertaken with the goal of applying novel, coordinated, scientific thinking and innovation to address the opioid crisis, this initiative builds on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implementation science to develop and test treatment models, and research to integrate behavioral interventions with medication-assisted treatment for OUD. With $500 million per year in dedicated federal funding for the initiative, NIH joins representatives from across the federal government, industry and academia for what the NIH Director, Dr. Collins, has termed an all-

[1345] https://www.cdc.gov/drugoverdose/.
[1346] https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics.

hands-on-deck approach to the emergency.[1347,1348] Through the NIH HEAL Initiative, NIH and its partners within HHS and the private sector aim to bring the best science to bear on this costly and debilitating public health crisis.

To achieve its goals, the NIH HEAL Initiative Research Plan focuses on two major areas: improving treatment for opioid misuse and enhancing pain management. The initiative includes more than 20 distinct programs led by 12 NIH ICs, reflecting an ambitious and crosscutting approach that acknowledges the interplay between pain and opioid misuse and the need to address both as part of the solution. Research projects are divided into six focus areas led by staff from across NIH and reflect the full spectrum of research, from basic research to implementation science. An Executive Committee composed of NIH leadership ensures coordination among the multiple projects and considers input from external advisory groups, including the HEAL Multidisciplinary Working Group and a Partnership Committee. This body of external experts was created to ensure strong and transparent processes between public and private sector groups involved in the NIH HEAL Initiative.[1349]

To prioritize the scientific strategies with the greatest potential for solutions, in FY 2017 and 2018, NIH brought together experts from government, industry, and academia for a series of three scientific meetings to inform the development of HEAL programs. These meetings focused on (1) Medications Development for Opioid Use Disorders and Overdose Prevention and Reversal; (2) Development of Safe, Effective, and Non-Addictive Pain Treatments; and (3) Understanding the Neurobiological Mechanisms of Pain.[1350–1352] Spanning disciplines and disease areas, the experts identified promising research programs that aligned with NIH HEAL Initiative research priorities.

Projects employ a range of approaches, including validation of new targets for pain therapeutics,[1353,1354] identification of individuals most at risk of overdosing,[1355,1356] and optimization of nonaddictive therapies to treat pain.[1357,1358] The initiative leverages infrastructure from NCATS to accelerate the development of novel small molecules and drug candidates to find new therapies for pain and opioid misuse and

[1347] https://www.nih.gov/news-events/news-releases/nih-launches-heal-initiative-doubles-funding-accelerate-scientific-solutions-stem-national-opioid-epidemic.
[1348] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative.
[1349] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/heal-initiative-research-plan.
[1350] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/executive-summary-medications-development-opioid-use-disorders-overdose-prevention-reversal.
[1351] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/executive-summary-development-safe-effective-non-addictive-pain-treatments.
[1352] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/executive-summary-understanding-neurobiological-mechanisms-pain.
[1353] https://heal.nih.gov/research/preclinical-translational/novel-targets.
[1354] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-18-042.html.
[1355] https://heal.nih.gov/research/preclinical-translational/biomarkers.
[1356] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-18-046.html.
[1357] https://heal.nih.gov/research/preclinical-translational/optimization-non-addictive-therapies.
[1358] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-19-010.html.

addiction.[1359] In addition to preclinical research, advancement of clinical research on pain management is a core goal of the initiative. For example, clinical trials in the Back Pain Consortium Research Program[1360] work in conjunction with the Early Phase Pain Investigation Clinical Network[1361] to understand common pain conditions, such as chronic low back pain, to improve diagnostic and treatment tools.[1362] Similarly, the Pain Management Effectiveness Research Network[1363] evaluates the effectiveness of pharmacologic and nonpharmacologic therapies to help establish evidence-based guidelines for treating pain.

To better understand how promising and evidence-based strategies and treatments might help more people with OUD, a suite of implementation science efforts will test the integration of evidence-based interventions in an array of settings. Among these studies is the HEALing Communities Study, an ambitious implementation study launched jointly by NIH and the Substance Abuse and Mental Health Services Administration (SAMHSA). The HEALing Communities Study aims to measure the impact of integrating evidence-based practices across multiple settings, including primary care, behavioral health, and the justice system. Three research sites and a data coordinating center focus on rural communities and have engaged strong partnerships with state and local governments and resources, such as police departments, faith-based organizations, and schools.[1364,1365]

These partnerships underscore the central role that communities are anticipated to assume in addressing the opioid crisis. As such, NIH IC communication offices, under the leadership of the OCPL within the NIH Office of the Director, are working together to increase awareness of the NIH HEAL Initiative and the agency's opioid research program. The cornerstone of these efforts is an agency-sponsored, dedicated initiative website for centralized news and program information.[1366] The website offers information about the NIH HEAL Initiative research plan and progress reports, events, and administrative information, including program governance and funding. OCPL also sponsors a robust NIH HEAL Initiative information plan designed to engage stakeholders and inform the extramural community about research opportunities and developments. Component elements of the plan include social media efforts, such as a September 2018 Twitter chat, a digital press kit and other resources for use by the media, and routine stakeholder announcements. Key announcements to date have focused on sharing information about the launch of partnership and advisory groups, announcing new research opportunities, and making available scientifically vetted, research-based health information.[1367] Specific research outcomes funded by NIH through the initiative are described further in this section.

In addition to the NIH HEAL Initiative, other trans-NIH activities have been implemented to address the opioid epidemic. Of note, OBSSR hosted the meeting *Contributions of Social and Behavioral Research in*

[1359] https://grants.nih.gov/grants/guide/rfa-files/RFA-TR-19-003.html.
[1360] https://grants.nih.gov/grants/guide/rfa-files/rfa-ar-19-026.html.
[1361] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-19-023.html.
[1362] https://heal.nih.gov/research/clinical-research.
[1363] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-19-021.html.
[1364] https://www.drugabuse.gov/drugs-abuse/opioids/nih-heal-initiative/healing-communities-study.
[1365] https://www.nih.gov/news-events/news-releases/nih-funds-study-four-states-reduce-opioid-related-deaths-40-percent-over-three-years.
[1366] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/research.
[1367] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/news-announcements.

Addressing the Opioid Crisis,[1368] bringing together experts from academia, government, and public health to identify key actionable social and behavioral science findings that can be applied immediately to address the opioid crisis and identify critical short-term research priorities, as well as potential mid-term and longer-term priorities that have the potential to improve the opioid crisis response. In a follow-up to the meeting, OBSSR launched a trans-NIH, Contributions of Social and Behavioral Research in Addressing the Opioid Crisis Strategic Planning Committee made up of senior-level staff from 23 NIH Institutes and Centers. This committee has been charged with integrating appropriate behavioral and social science research priority recommendations from their meeting into current and future NIH activities.

Tobacco Regulatory Science Program

Another area of cross-agency collaboration is the science of tobacco product regulation. The Tobacco Regulatory Science Program (TRSP) coordinates the trans-NIH collaboration with the FDA Center for Tobacco Products (CTP) to conduct research supporting FDA regulation of tobacco products.[1369] As of FY 2018, CTP and NIH have jointly developed 37 FOAs and funded a total of 294 grants. The U54 Tobacco Centers of Regulatory Science, first funded in 2013, are the centerpiece of this partnership. NIH and FDA renewed their commitment to the U54 Tobacco Centers of Regulatory Science program in 2018, committing more than $151 million in total funding to support nine specialized centers for the next 5 years. The awards are administered by NCI, NHLBI, and NIDA.

TRSP research advances a scientific understanding of tobacco product toxicity, addiction, health effects, behaviors, communication, marketing, and the impact of potential FDA regulations, as well as provides rapid-response findings on time-sensitive research topics.[1370–1373] Furthermore, to ensure the existence of a skilled workforce knowledgeable regarding research in tobacco regulations, TRSP also funds specific training awards and small grant programs to encourage investigators to initiate research in this area.[1374–1380]

Among the research supported by TRSP is that on Electronic Nicotine Delivery Systems (ENDS) or e-cigarettes. ODP—with collaboration from NCI, NIDA, NIDCR, NIEHS, and NIMHD—provides support for a subgroup of the NIH Tobacco and Nicotine Research Interest Group focused on specific needs related to e-cigarette and vaping issues. ENDS are battery-powered inhalation devices designed to deliver to the

[1368] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/events.
[1369] https://prevention.nih.gov/tobacco-regulatory-research/funded-research/funded-research-tobacco-centers-regulatory-science.
[1370] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-019.html.
[1371] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-17-013.html.
[1372] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-17-002.html.
[1373] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-17-006.html.
[1374] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-18-005.html.
[1375] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-18-006.html.
[1376] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-18-007.html.
[1377] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-18-008.html.
[1378] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-17-012.html.
[1379] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-17-014.html.
[1380] http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-15-004.html.

user an aerosol typically containing nicotine. Information is limited on the safety of the devices and the aerosols they generate, how changes in the devices or aerosols affect nicotine delivery, and how these differences affect biological systems and behavior. As such, more research is needed to understand the potential risks and benefits of ENDS use at the molecular, cellular, physiological, and behavioral levels. To this end, ODP coordinated the release of two trans-NIH FOAs to encourage research evaluating the biological mechanisms whereby ENDS aerosols affect the normal and disease states relevant to human cells, tissues, or organs.[1381,1382] In addition, ODP coordinated the release of two additional trans-NIH FOAs to address gaps around the effects of e-cigarettes on use of other tobacco products, alcohol, and other substances from a population, clinical, or applied perspective.[1383,1384]

TRSP-funded research found that, when reducing the nicotine content of cigarettes, immediate nicotine reduction led to greater decreases in smoking compared to gradual reduction over time. Immediate reduction was also associated with less overall exposure to cigarette-related toxicants and greater reductions on dependence measures, suggesting that a policy implementing immediate reduction would provide a greater public health benefit.[1385]

Complementing this finding, a study by NIDA-supported researchers found that e-cigarette use in high school students was associated with subsequent use of conventional cigarettes.[1386] The reverse (cigarette use preceding e-cigarette use) was not found. This study supports other recent research suggesting that e-cigarettes may increase risk of cigarette smoking in teens.[1387] In a population-based prospective cohort study, researchers found that adult smokers who used e-cigarettes daily at some point during the study period were less likely to quit smoking than nonusers of e-cigarettes.[1388]

A study funded by TRSP also examined human airway samples to explore effects of e-cigarette use on airways. Researchers found that use of ENDS alters the profile of innate defense proteins in airway secretions, inducing some changes that are similar to those produced by cigarette smoking, as well as some that are unique to ENDS use.[1389]

Investigators found that acute exposure to aerosol from heated tobacco products (also called heat-not-burn products) impairs vascular endothelial function to the same extent as cigarette smoke, suggesting that these products do not avoid the adverse cardiovascular effects of smoking cigarettes.[1390] Beyond direct toxicity effects, TRSP research has also examined longer-term health effects. Researchers studied the association between e-cigarette use and cigarette smoking and myocardial infarction. Daily e-cigarette

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[1381] https://grants.nih.gov/grants/guide/pa-files/PAR-17-475.html.
[1382] https://grants.nih.gov/grants/guide/pa-files/PAR-17-476.html.
[1383] https://grants.nih.gov/grants/guide/pa-files/PAR-18-847.html.
[1384] https://grants.nih.gov/grants/guide/pa-files/PAR-18-848.html.
[1385] Hatsukami DK, et al. *JAMA* 2018;320(9):880-91. PMID: 30193275 .
[1386] Bold KW, et al. *Pediatrics* 2018;141(1).pii: e20171832. PMID: 29203523.
[1387] https://www.drugabuse.gov/about-nida/noras-blog/2018/01/nidas-past-year-achievements-point-way-toward-future-advances.
[1388] Weaver SR, et al. *PLoS One* 2018;13(7):e0198047. PMID: 29985948.
[1389] Reidel B, et al. *Am J Respir Crit Care Med* 2018;197(4):492-501. PMID: 29053025.
[1390] Nabavizadeh P, et al. *Tob Control* 2018;27(Suppl 1):s13-s19. PMID: 30206183.

use, adjusted for smoking cigarettes as well as other risk factors, is associated with increased risk of myocardial infarction.[1391]

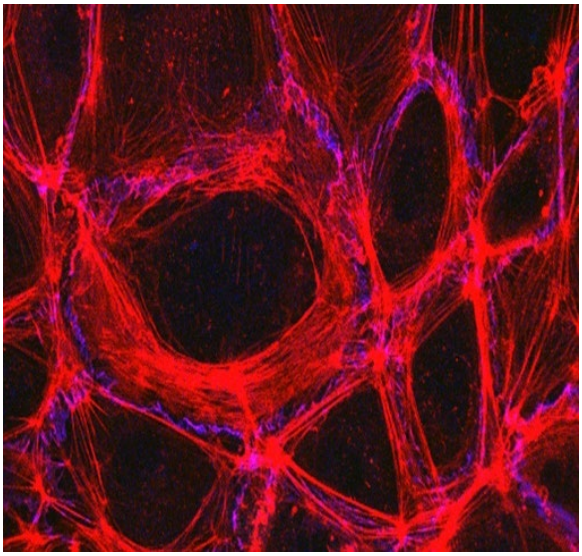

Figure 76. The structure of the endothelium, the thin layer of cells that line our arteries and veins, is visible here. The endothelium is like a gatekeeper, controlling the movement of materials into and out of the bloodstream. Endothelial cells are held tightly together by specialized proteins that function like strong ropes (red) and others that act like cement (blue). Credit: Christopher V. Carman and Roberta Martinelli, Harvard Medical School, Boston, MA.

A multitude of compounds are available for use with ENDs. To understand the variety of potential effects, researchers funded by TRSP evaluated more than 7,700 commercially available flavored e-liquids. Researchers developed a high-throughput screening method to rapidly triage compounds and measure their toxicity.[1392] In this study, vanillin or cinnamaldehyde was associated with higher toxicity values. To effectively share this information, TRSP-funded researchers developed a publicly available website of chemical and toxicity data.[1393]

Understanding Prevalence, Risk Factors, and Underlying Biology

Beyond opioids and tobacco, SUD also includes consideration for the use of a variety of other substances. However, the prevalence, risk factors, and underlying biology of each may differ. Research in this area provides insight into how the human body and brain function, both under the influence of and in the absence of these substances. NIH funds research across many substances and for considerations across differing severities of use, misuse, and addiction. NIH supports research to estimate the prevalence of SUD and to understand how individuals come to be exposed to and subsequently use or misuse said substances.

[1391] Alzahrani T, et al. *Am J Prev Med* 2018;55(4):455-61. PMID: 30166079.
[1392] Sassano MF, et al. *PLoS Biol* 2018;16(3):e2003904. PMID: 29584716.
[1393] https://eliquidinfo.org.

To obtain up-to-date and comprehensive data on drug use, NIDA launched the National Drug Early Warning System (NDEWS) in 2014. NDEWS represents a novel approach to monitoring and responding to emerging drug trends, including innovative components to increase timeliness and public health impact. NDEWS has built a virtual NDEWS Network of more than 1,800 members, which serves as a crowd-sourced or citizen scientist approach to identifying new drugs or drug problems, a mechanism for disseminating information, and a forum for exchanging information and sharing research and intervention tools and approaches. NDEWS can also rapidly undertake and disseminate findings from field studies to investigate hot spots of such drug problems as increases in opioid overdoses. NDEWS optimizes NIDA's current research investments by collaborating with local NIDA-supported researchers in undertaking hot-spot field studies, thereby facilitating entry into local research contexts.

For example, a hot-spot study was conducted in New Hampshire in 2016 and 2017 to examine the very high level of opioid overdoses in the state. It included the establishment of the geographic distribution and demographic profile of deaths, interviews with drug users and first responders to understand patterns of use and response to overdoses, and in-depth review of death records and toxicological analysis of existing decedent urine specimens using state-of-the-art methods to reveal drugs at the time of death. Study reports were shared with local health officials and released promptly on the NDEWS website as they were finalized. The type of information generated by NDEWS is a critical epidemiological instrument that allows the development of rapid, informed, and effective public health responses that can then be deployed precisely where and when they are needed.[1394]

NIAAA collaborated with the Office of the Surgeon General, SAMHSA, NIDA, and other federal partners in the development of *Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health,* which was released in November 2016. It is the first-ever Surgeon General's Report on this topic and addresses alcohol, illicit drug, and prescription drug misuse in the context of neurobiology, prevention, treatment, recovery, and health systems integration.[1395,1396]

NIDA leads the NIH Pain Consortium Centers of Excellence in Pain Education, 12 centers working to enhance patient outcomes by improving the education of health care professionals about pain and its treatment. The centers act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, and pharmacy schools to improve how health care professionals are taught about pain and its treatment.[1397]

Addressing the prescription of pain medication is one critical strategy in tackling the epidemic of opioid use, since prescriptions are one means by which individuals become exposed to opioids. NIA-supported investigators have found that physicians are prescribing more opioid pain medicines than ever before to patients undergoing common, low-risk surgeries. The study analyzed insurance claims from 2004 through 2012 for more than 155,000 adults undergoing four common outpatient surgical procedures—carpal

[1394] https://www.drugabuse.gov/related-topics/trends-statistics/national-drug-early-warning-system-ndews
[1395] https://addiction.surgeongeneral.gov/.
[1396] https://www.niaaa.nih.gov/news-events/news-noteworthy/surgeon-general-issues-landmark-report-alcohol-drugs-and-health.
[1397] https://painconsortium.nih.gov/Funding_Research/CoEPEs.

tunnel repair, laparoscopic gall bladder removal, some minimally invasive knee surgeries, and hernia repair.[1398] In an analysis of patients who had not received an opioid prescription in the 6 months before surgery, the researchers observed that four out of every five patients in the study filled a prescription for an opioid pain medicine within 7 days after surgery. The percentage of patients who got those drugs increased over the period studied for all four surgical procedures. Notably, the amount of opioid medicine dispensed to patients after surgery also increased markedly between 2004 and 2012 for all procedures studied. Among patients undergoing knee arthroscopy, for example, the investigators estimated a greater than 18 percent increase in the average total amount of opioid dispensed, driven by a change in the average daily dose. In the context of a major opioid epidemic, the increasing prescription of opioids to lower-risk patients with minor surgery is a concerning trend.

Examining the same among children, NICHD-supported researchers evaluated trends in opioid prescriptions dispensed to individuals 18 years or younger between 2004 and 2017 using data from a large national insurance company. In 2004, an average of 3.3 of every 1,000 children younger than 18 received an outpatient opioid prescription in a given month. This increased by 24 percent to 4.1 of every 1,000 children during the period between 2009 and 2012, and then dropped even more dramatically, to 2.1 per 1,000 children at the beginning of 2017. A similar trend was observed for long-term opioid use.[1399] Opioid use early in life is associated with several health risks and also is related to a higher likelihood of opioid misuse in the future.

Opioid use may also have other consequences. Opioid treatment may affect the rate of healing in chronic wounds. Reduced pain is a sign of healing in patients with chronic wounds, suggesting that molecular mechanisms involved in opioid pain treatments may play a role in wound healing. Pain control can also facilitate wound care procedures. However, reduced immune activity that sometimes accompanies opioid treatment may adversely affect wound healing.[1400] Clinical and wound outcome data were analyzed from the Wound Etiology and HEALing study (WE-HEAL), which follows patients with chronic wounds over time. Although the number of chronic wounds that finally healed or did not heal was equivalent between patients who received opioid pain medicine and those who did not, the time to healing was significantly shorter for those who had never received opioids. Patients receiving higher opioid doses due to larger wound size or painful comorbidities, such as lymphedema or sickle cell disease, had slower wound healing than those receiving lower doses or no opioids. The WE-HEAL findings raise important considerations in clinical management of chronic wounds.

Among other segments of the U.S. population, adolescents are of particular interest. NIH funds a number of studies to gather information on U.S. adolescents, including information on their health behaviors and substance use.

NICHD's Division of Intramural Population Health Research coordinates the NEXT Generation Health Study, a nationally representative cohort of 2,874 adolescents, recruited in 2010 and assessed annually

[1398] Wunsch H, et al. *JAMA* 2016;315(15):1654-7. PMID: 26978756.
[1399] Gagne JJ, et al. *JAMA Pediatr* 2019;173(1):98-9. PMID: 30419137.
[1400] Shanmugam VK,, et al. *Wound Repair Regen* 2017;25(1):120-30. PMID: 27865036.

until they reach the age of 22 years for health; cardiovascular risk factors; and adolescent diet, physical activity, sleep, and driving behaviors. Conducted in collaboration with NIAAA, this study provides a means to monitor the prevalence of substance abuse among adolescents.[1401] NIDA funds the annual Monitoring the Future Survey, which measures drug and alcohol use and related attitudes among adolescent students nationwide. Survey participants report their drug use behaviors across three time periods: lifetime, past year, and past month. Overall, more than 44,000 students from nearly 400 public and private schools participated in the 2018 Monitoring the Future survey. Findings are released annually and help provide researchers and policymakers a better understanding of which drugs are used by teens and young adults, how they are obtained and used, and attitudes among teens about the safety and ease of obtaining such drugs.[1402]

The Add Health Study, formerly the National Longitudinal Study of Adolescent Health and also known as the National Longitudinal Survey of Adolescent to Adult Health, is the largest longitudinal study of adolescents ever undertaken. Led by NICHD and with collaboration from NIA, the Add Health study has yielded scientific advances that have helped identify trends and differences among groups in adolescent risk behavior. Many previous studies have examined how much friends' drinking habits or the price of alcohol influence underage drinking. However, none have examined both of these factors together. Using interviews from students at 16 high schools and information from the National Longitudinal Survey of Adolescent to Adult Health, researchers found that high schoolers whose peers drank were much more likely to drink themselves, regardless of the price of alcohol. Peer influence did not affect how often kids drank or whether they binge drank. Contrary to other studies on underage drinking, this study found that alcohol's cost was not a determining factor in whether high schoolers drank. The researchers concluded that access to alcohol is a larger hurdle for high schoolers than price.[1403,1404]

A national study also enabled researchers to identify differences in prescription opioid misuse among adolescents by geographic locale. Researchers used data from a nationally representative survey of over 30,000 adolescents to assess prescription opioid misuse in adolescents ages 12 to 17. An estimated 6.8 percent of rural teens and 5.3 percent of teens in large urban areas reported misusing opioids in the previous year. Rural adolescents perceived substance use to be less risky and were more likely to smoke and engage in binge drinking. However, they were less likely to use marijuana. Regardless of whether they lived in a rural or urban area, teens who misused opioids most commonly reported the source of the drug as friends and family. However, rural teens were more likely than urban teens to report having received opioids from a physician or dealer. These results may help public health officials improve programs to decrease opioid misuse, particularly in rural areas.[1405]

To capture the effects of substance use on mortality, NLM started an effort in FY 2018 toward modernizing the systems for capturing drug death data from death certificates. The goals of this effort are to (1) advise the National Center for Health Statistics on strategies to extract, categorize, and map drug-related strings,

[1401] https://www.nichd.nih.gov/about/org/diphr/officebranch/sbsb/next.
[1402] https://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future.
[1403] https://www.cpc.unc.edu/projects/addhealth.
[1404] Ajilore O, et al. *Econ Hum Biol* 2016;23:76-83. PMID: 27507725.
[1405] Monnat SM, et al. *J Rural Health* 2016;32(2):204-18. PMID: 26344571.

terms, and phrases from death certificate records' literal text to classification systems used by researchers; (2) establish mapping between information technology systems that assures classification standards are used with respect to clinical terminologies; and (3) develop natural language processing (NLP) programs that reduce manual processes in classifying new drug terms identified on death certificates.[1406]

Another population that is particularly vulnerable and for whom long-term consequences are associated with substance use includes pregnant women and fetuses in utero. Supported by NIAAA, NICHD, NIDA, and NIMH, an analysis of national survey data on 12,988 pregnant women, ages 18 to 44 years, found that use of alcohol during pregnancy declined between 2002 and 2016 from 9.59 percent to 8.43 percent. During the same period, cigarette use declined from 17.59 percent to 10.3 percent. In contrast, researchers found a slight increase in cannabis use by pregnant women, from 2.85 percent to 4.9 percent. These findings raise concern, suggesting the need for increasing public awareness about the consequences of prenatal exposure to cannabis to the health of children.[1407]

This increase in cannabis use among pregnant women may be explained by the trend of marijuana legalization, resulting in reports of more pregnant women using marijuana recreationally or to treat nausea and vomiting during pregnancy. Using data from the NICHD-funded Stillbirth Collaborative Research Network and adjusting for tobacco use, illicit drug use, BMI, and socioeconomic factors, researchers found maternal marijuana use was associated with an increased risk in overall neonatal morbidity, including admission to the neonatal intensive care unit, diagnosis of pulmonary conditions, and other neonatal conditions.[1408]

NIAAA supports the Collaborative Initiative on FASD, a multidisciplinary consortium of domestic and international projects that encompasses basic, clinical, and translational FASD research projects. During pregnancy, alcohol can pass through the placenta and umbilical cord into the developing fetus. The toxic effects of alcohol on the developing fetus can lead to poor growth, as well as later problems in behavior, attention, and learning. These conditions, known collectively as FASD, are the most common preventable cause of intellectual disability. In a study assessing 6,000 first-graders across four U.S. communities, the consortium has shown that a significant number of children have FASD, with conservative rates ranging from 1 to 5 percent.[1409,1410] These new findings represent more accurate prevalence estimates of FASD among general U.S. communities than prior research.

A growing body of evidence indicates that some effects of alcohol use are unique to women, even those who are not pregnant. Women have higher susceptibility to short- and long-term alcohol-related consequences, and studies have shown that alcohol use and misuse among women is increasing.

[1406] Kho SJ, et al. *Stud Health Technol Inform* 2019;264:183-7. PMID: 31437910.
[1407] Agrawal A, et al. *JAMA Pediatr* 2019;173(1):95-6. PMID: 30398527.
[1408] Metz TD, et al. *Am J Obstet Gynecol.* 2017;217(4):478.e1-478.e8. PMID: 28578174.
[1409] https://www.niaaa.nih.gov/news-events/news-releases/study-first-graders-shows-fetal-alcohol-spectrum-disorders-prevalent-us.
[1410] May PA, et al. *JAMA* 2018;319(5):474-82. PMID: 29411031.

For example, a 2017 NIAAA analysis of data from the NHIS demonstrated that current drinking and binge drinking among adults age 60 and older increased from 1997 to 2014 more significantly among women than men. To bring attention to this public health issue, NIAAA was the lead sponsor in 2017 of the *National Conference on Alcohol and Opioid Use in Women and Girls: Advances in Prevention, Treatment and Recovery Research*. The purpose of this conference was to gather general health care providers, addiction and treatment professionals, health policymakers, and addiction researchers to highlight the latest research on substance misuse among females and promote coordinated approaches for addressing it.[1411,1412]

A 2018 NIAAA study found that the rate of alcohol-related visits to U.S. EDs increased by nearly 50 percent between 2006 and 2014, especially among females and drinkers who are middle-aged and older. The findings suggest that more individuals are consuming alcohol in ways that lead to medical emergencies.[1413,1414] High-intensity drinking refers to consumption of two or more times the gender-specific thresholds for binge drinking, which is 10 or more standard drinks for males and 8 or more for females. A 2017 NIAAA study found that this drinking pattern is associated with an elevated risk of ED visits and other adverse consequences. In FY 2018, NIAAA formed a working group of external experts to better understand the social and cultural determinants of high-intensity drinking and to inform research efforts in this area.[1415–1417]

Alcohol misuse can lead to alcohol-associated liver diseases (AALD), a group of serious and potentially fatal conditions that include fatty liver, alcoholic hepatitis, cirrhosis, and liver cancer. Alcohol misuse now accounts for nearly 50 percent of all liver disease deaths in the U.S. NIAAA supports efforts across the translational science continuum to diagnose, prevent, and treat AALD, including basic research that has identified numerous molecular targets in liver inflammation that may have therapeutic potential for AALD. In FY 2018, NIAAA participated in a workshop with FDA and the American Association for the Study of Liver Diseases to address challenges in AALD clinical trial design and drug development. In parallel, NIAAA established an Alcoholic Hepatitis Clinical and Translational Network to streamline processes for designing, initiating, and conducting clinical trials of promising therapeutics.[1418]

[1411] https://www.niaaa.nih.gov/news-events/news-noteworthy/niaaa-host-conference-alcohol-and-opioid-use-women-girls-oct-26-27.
[1412] https://www.niaaa.nih.gov/2017-national-conference-alcohol-and-opioid-use-women-girls.
[1413] https://www.niaaa.nih.gov/news-events/news-releases/nih-study-shows-steep-increase-rate-alcohol-related-er-visits.
[1414] White AM, et al. *Alcohol Clin Exp Res* 2018;42(2):352-9. PMID: 29293274.
[1415] https://www.niaaa.nih.gov/news-events/news-releases/study-finds-tens-millions-americans-drink-alcohol-dangerously-high-levels.
[1416] Hingson RW, et al. *Am J Prev Med* 2017;52(6):717-27. PMID: 28526355.
[1417] https://www.niaaa.nih.gov/news-events/meetings-events-exhibits/high-intensity-drinking-working-group-meeting.
[1418] https://www.niaaa.nih.gov/research/niaaa-research-highlights/register-fda-niaaa-aasld-workshop-clinical-trial-design-and.

NIAAA collaborated with Home Box Office (HBO) to produce *Risky Drinking*, a documentary that premiered in December 2016. *Risky Drinking* spotlights alcohol use disorder (AUD) through the stories of four people whose drinking has profoundly impacted their lives.[1419–1421]

AUD is a highly heterogenous disorder. Affected individuals differ in their drinking patterns, motivations for drinking, and clinical signs and symptoms, as well as the neurobiological, genetic, and environmental factors that contribute to alcohol misuse. The NIAAA Intramural Research Program is developing the Addictions Neuroclinical Assessment to assess and classify individual differences in AUD based on key neurofunctional domains within the addiction cycle. Improved understanding of individual differences could enable more precise diagnosis of the specific deficits or other drivers that underlie an individual's AUD and, in turn, help target behavioral and/or pharmacological therapy to a person's specific problem(s), thereby increasing the effectiveness of AUD treatment.[1422,1423]

Particularly among adolescents, greater insight can improve long-term outcomes. Many approaches are applied to gaining these insights, including studying the biology underlying these processes using animal models and population-based studies of human adolescents and children.

Since 2010, NIAAA has supported the Neurobiology of Adolescent Drinking in Adulthood Consortium, which aims to define the neurobiological mechanisms underlying the effects of adolescent alcohol exposure on adult brain function and behavior using rodent models. During the first phase of the Consortium, several seminal findings were reported suggesting that adolescent alcohol exposure may lead to long-lasting brain and behavioral changes in adulthood. In its current phase, the Consortium is building upon these findings to further investigate the mechanisms through which adolescent alcohol exposure affects brain maturation and adult brain function.[1424,1425]

Launched in FY 2012, NIAAA's National Consortium on Alcohol and Neurodevelopment in Adolescence is a multisite longitudinal study designed to elucidate the effects of alcohol exposure on the developing adolescent human brain and to identify brain characteristics that may predict AUD and related problems. With collaboration from NICHD, NIDA, and NIMH, the five sites have enrolled more than 800 youth, ages 12 to 21, and recent study results have indicated that adolescents who drink alcohol heavily have altered brain development trajectories compared to adolescents who abstain or consume lower levels of alcohol. In FY 2017, NIAAA renewed the Consortium for a second period of funding.[1426–1428] The National

[1419] https://www.niaaa.nih.gov/news-events/news-noteworthy/niaaahbo-documentary-risky-drinking-spotlights-alcohol-use-disorder.
[1420] https://www.niaaa.nih.gov/hbo.
[1421] https://www.hbo.com/documentaries/risky-drinking.
[1422] https://www.niaaa.nih.gov/news-events/news-releases/scientists-propose-neuroscience-framework-diagnosing-addictions.
[1423] Kwako LE, et al. *Biol Psychiatry* 2016;80(3):179-89. PMID: 26772405.
[1424] https://www.med.unc.edu/alcohol/nadiaconsortium/.
[1425] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-15-006.html.
[1426] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-17-003.html.
[1427] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-17-004.html.
[1428] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-17-005.html.

Consortium on Alcohol and Neurodevelopment in Adolescence laid the foundation for the larger and more extensive ABCD study.[1429]

Launched in September 2015, the ABCD study is the largest long-term study of brain and cognitive development in children in the U.S.[1430,1431] ABCD is following 9- and 10-year-old children into early adulthood to determine how environmental, social, genetic, and other biological factors influence brain structure, function, and other health outcomes, including substance use. ABCD was initiated by the Collaborative Research on Addiction partnership at NIH (NCI, NIAAA, NIDA), which is leading this effort in partnership with NHLBI, NICHD, NIMH, NIMHD, NINDS, OBSSR, ORWH, the National Endowment for the Arts, the National Institute of Justice, the NSF, and the CDC Division of Adolescent and School Health and Division of Violence Prevention. On December 3, 2018, NIH announced the completion of enrollment for the ABCD study, with 11,874 youth participating in the study.[1432,1433]

The ABCD study is being conducted at 21 research sites around the country and will use advanced neuroimaging to observe brain development in children throughout adolescence, while tracking social, behavioral, physical, and environmental factors that may affect brain development and other health outcomes. Imaging and assessment data from the first 4,500 participants have been made available to researchers through the NIMH Data Archive.[1434] ABCD-derived data will enable researchers to better understand the myriad factors that contribute to brain and cognitive development and how alcohol and other drugs affect these processes.

Anonymized study data from the ABCD study are made available to the broad research community on a regular basis, allowing scientists to analyze data and ask novel questions that were not even anticipated in the original study planning. Offering these data while the study is in progress means that both ABCD investigators and non-ABCD researchers will have access to the datasets to pursue a variety of research interests. To help researchers rigorously analyze the rich datasets generated by the ABCD Study, NIDA developed the ABCD Data Exploration and Analysis Portal (DEAP). The DEAP allows users to analyze ABCD study data online, while providing appropriate statistical models and tools that take advantage of the study design. The DEAP code is publicly available and open source, allowing researchers to freely use, modify, and improve it.[1435]

In addition to these important initiatives focused on adolescent and child development, the NIH HEAL Initiative also has components that prioritize understanding cognition, behavior, and social and emotional development among children. Led by NIDA, the HEALthy Brain and Child Development Study supports

[1429] http://ncanda.org/.
[1430] https://www.addictionresearch.nih.gov/abcd-study.
[1431] https://www.nih.gov/news-events/news-releases/nih-releases-first-dataset-unprecedented-study-adolescent-brain-development.
[1432] https://www.nih.gov/news-events/news-releases/abcd-study-completes-enrollment-announces-opportunities-scientific-engagement.
[1433] https://www.drugabuse.gov/news-events/news-releases/2018/12/abcd-study-completes-enrollment-announces-opportunities-scientific-engagement.
[1434] https://data-archive.nimh.nih.gov/abcd.
[1435] https://abcdstudy.org/scientists_data_sharing.html.

development of a large-scale, multisite research study to prospectively examine the human brain and understand the long-term impacts of pre- and postnatal drug exposure. The information collected will inform how adverse environmental exposures on brain and behavioral health relate to risk for substance use and mental disorders.[1436]

Another HEAL Initiative effort underway, Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW), aims to inform clinical care for newborns with neonatal opioid withdrawal syndrome (NOWS). The study is a collaboration between NICHD's NRN, which has more than 30 years of experience in conducting clinical trials with newborns and the (ISPCTN), part of the Environmental influences on Child Health Outcomes (ECHO) program within the NIH Office of the Director.

As part of the ACT NOW initiative,[1437] the two networks completed the ACT NOW Current Experience study, a medical record review of the birth hospitalizations for more than 1,800 mother–infant dyads with neonatal opioid withdrawal syndrome across 30 sites within the ISPCTN and NRN. Investigators are currently analyzing these data. In addition, the two networks began developing two large multicenter clinical trials to improve care for infants with NOWS, which will begin in 2020 as part of the NIH HEAL Initiative. One trial compares the "Eat, Sleep, Console" assessment and nonpharmacologic treatment–focused approach to caring for infants with NOWS to usual care. The second trial compares two approaches to weaning infants from opioids using opioid replacement therapy with morphine or methadone for treatment of NOWS. The overall goal of these trials is to find innovative ways to identify and treat newborns exposed to opioids, thus improving their cognitive and health outcomes.[1438,1439]

As one component of this study, chart abstraction for the ACT NOW Current Experience (ACT NOW CE) study has been completed. The ACT NOW CE study is a medical record review of more than 1,800 neonates across 30 sites who have been exposed to opioids in utero. Researchers hope to better understand the care provided to neonates with NOWS. These data will allow researchers to identify gaps in care and will provide information needed to design future clinical trials to explore innovations in care.

Also as part of the ACT NOW initiative, NICHD launched a FOA for an Antenatal Opioid Exposure Longitudinal Study Consortium, calling for a prospective longitudinal cohort study examining newborns exposed to opioids in utero compared with those not exposed to better understand the long-term effects of antenatal opioid exposure and NOWS.[1440] It is expected that the results will point to targets for intervention trials to improve outcomes for these vulnerable infants.

Our understanding of the biological effects of opioid use and, more broadly, substance use and addiction has expanded through investment in research and paints a picture of the complexity of factors involved in and leading up to addiction and its aftermath. Opioids produce their effects by binding to specific

[1436] https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-19-029.html.
[1437] https://www.nichd.nih.gov/newsroom/releases/100217-ACTNOW.
[1438] https://www.nih.gov/news-events/news-releases/nih-funded-study-focus-newborns-affected-opioids.
[1439] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/heal-initiative-research-plan.
[1440] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-19-025.html.

receptors that engage multiple cellular signaling pathways. Recent evidence from research supported by NIDA and NINDS shows that different opioids can exhibit a bias toward a specific signaling pathway, which determines their ability to produce certain side effects, such as respiratory depression. NIDA-funded research is examining this bias and using it to guide the development of safer analgesics.[1441]

NIH-supported researchers found that the antidepressant ketamine activates the brain's opioid system, as well as the glutamate system. This finding highlights the interaction between depression, pain, and opioid addiction, three major public health issues.[1442,1443]

Although the full range of changes in brain function that perpetuate opiate addiction is unclear, researchers discovered that in people and mice, long-term opiate exposure leads to increased numbers of hypocretin neurons, a cell type in the brain that regulates sleep/wake and appetite.[1444] In June 2018, neuroscientists studying narcolepsy reported on their serendipitous discovery that post-mortem brains from individuals who had been addicted to heroin show greatly increased numbers of neurons producing the neuropeptide hypocretin (also known as orexin). They found that hypocretin helps regulate wakefulness and appetite, and a diminished number of cells in the brain producing it is associated with narcolepsy. Replicating this finding from humans, researchers studied the effects of opiates in a mouse model and found that mild chronic opiate exposure did indeed restore hypocretin neurons. These results suggest that increases in these cells and in brain hypocretin could underlie the complaints of sleep problems in patients with OUD.

In June 2018, a team of NIDA-funded researchers reported that they had developed a genetically encoded biosensor that could both detect activation of opioid receptors and map the differences in activation within living cells produced by different opioids.[1445] They found that opioids bind to receptors on structures within the cell and not just on the cell membrane—a novel finding in itself. In addition, the team also discovered striking differences in how synthetic opioids interact with these structures in comparison to similar compounds produced by a person's own body. Whereas compounds produced by a person's own body activated receptors on a part of the cell called endosomes, synthetic opioid drugs activated receptor sites on a separate structure called the Golgi apparatus. These very different patterns of activation within the cell may lead to greater understanding of why non-peptide opioid drugs produce tolerance, as well as of the behavioral changes seen with opioid misuse and addiction in contrast to the opioid peptides produced by the body.

The long-lasting nature of the behavioral changes seen in SUDs suggests that changes in patterns of how genes are expressed are occurring in the brain. Independent lines of research have shown that these processes play a crucial role in influencing the lasting effects of drugs on the brain. Researchers have conducted animal studies that show that repeated exposure to drugs can cause such changes in the brain's

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[1441] Schmid CL, et al. *Cell* 2017;171(5):1165-75.e13. PMID: 29149605.
[1442] http://med.stanford.edu/news/all-news/2018/08/ketamines-antidepressive-effects-tied-to-opioid-system-in-brain.html.
[1443] Williams NR, et al. *Am J Psychiatry* 2018;175(12):1205-15. PMID: 30153752.
[1444] Thannickal TC, et al. *Sci Transl Med* 2018;10(447). pii: eaao4953. PMID: 29950444.
[1445] Stoeber M, et al. *Neuron* 2018;98(5):963-76.e5. PMID: 29754753.

reward regions. Furthermore, in some cases, researchers have demonstrated a direct link between those changes, gene expression, and addiction-related behavioral problems. These studies are providing a new view of the range of genes and noncoding regions of DNA that are affected by repeated drug exposure and the precise molecular basis of that effect. NIDA is a leading member of the NIH Common Fund's Epigenomics Program, which includes a series of complementary initiatives that have generated new research tools, technologies, datasets, and infrastructure to accelerate our understanding of how genomewide chemical modifications to DNA regulate gene expression—without altering the DNA sequence itself—and what role these modifications play in health and disease.[1446]

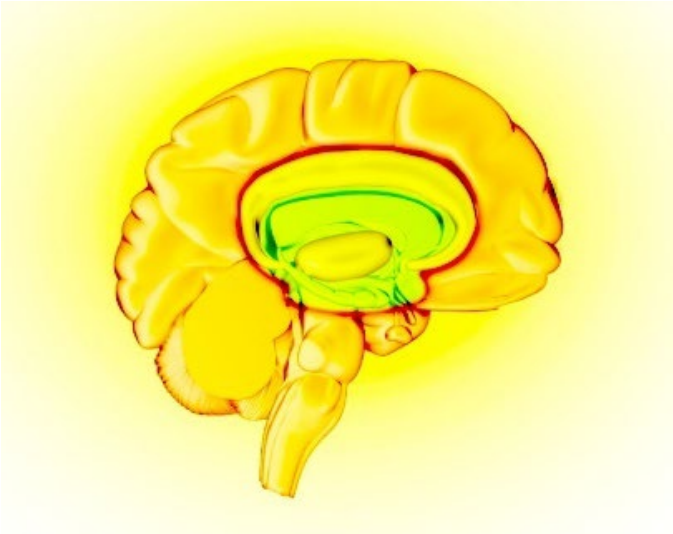

Figure 77. A graphic highlighting the brain's reward circuit. Credit: NIDA.

Improving Treatment and Prevention

A deeper understanding of the effects and dependencies in substance use and addiction improves the ability to treat SUDs.

Treatment

Although methadone, buprenorphine, and naltrexone have been used to treat OUD, it is not known whether they can reduce the risk of death after a non-fatal overdose. Using hospital and death records, CTSA program and NIDA-funded researchers examined this question. They found that less than a third of those who had a non-fatal opioid overdose received these drugs. However, those who were treated with methadone or buprenorphine were less likely to die from opioid-related causes. No association was

[1446] https://commonfund.nih.gov/epigenomics.

identified between risk of death and naltrexone treatment. The results suggest that people at high risk of death from opioid overdose may benefit from such medications.[1447,1448]

NIDA has provided scientific support to help develop two extended-release formulations of buprenorphine, the fastest-growing evidence-based medication for OUD. Extended-release formulations can help patients both adhere to a treatment regimen and be retained in treatment in general. One of these formulations, an implanted version called probuphine, was approved in May 2016.[1449] In May 2018, FDA approved lofexidine, the first medication targeted specifically to treat the physical symptoms associated with opioid withdrawal. NIDA's medications development program helped fund the science leading to the drug's approval, which could benefit the thousands of Americans seeking medical help for their opioid addiction by helping them adhere to their detoxification or treatment regimens.[1450]

Figure 78. Researchers at the National Institute on Drug Abuse (NIDA) are working to identify new medications for treating drug addiction. Credit: NIDA.

More broadly, NIDA's overarching mission is to allow treatment providers, researchers, patients, and NIDA to cooperatively develop new treatments.[1451] As such, NIDA funds the National Drug Abuse Clinical Trials Network (CTN), which comprises 13 research centers with 25 principal investigators affiliated with

[1447] https://www.nih.gov/news-events/nih-research-matters/medications-reduce-risk-death-after-opioid-overdose.
[1448] Larochelle MR, et al. *Ann Intern Med* 2018;169(3):137-45. PMID: 29913516.
[1449] https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm503719.htm.
[1450] https://www.drugabuse.gov/about-nida/noras-blog/2018/05/nida-supported-science-leads-to-first-fda-approved-medication-opioid-withdrawal.
[1451] https://www.drugabuse.gov/about-nida/organization/cctn/ctn.

academic medical centers and large health care networks, 2 research coordinating centers, and more than 240 community-anchored treatment programs and/or medical settings in more than 40 states, the District of Columbia, and Puerto Rico. As part of the NIH HEAL Initiative, NIDA released a FOA that invites applications from new clinical investigators to participate in the CTN.[1452] The ongoing opioid epidemic and crisis of overdose deaths present an urgent public health need to quickly expand the CTN to increase the network's scientific and clinical research capabilities and to better cover geographic regions across the U.S. and regions most impacted by the opioid overdose epidemic.

This same CTN conducted a study to compare Vivitrol® (extended-release naltrexone) to Suboxone® (buprenorphine and naloxone) Sublingual Film for patients addicted to heroin or other opioids, including prescription pain relievers. Contrary to the assumption that outcomes would be better with buprenorphine than with extended-release naltrexone, this study showed that among patients who were able to successfully initiate treatment with extended-release naltrexone following the initial hurdle of detoxification (a prerequisite for starting antagonist treatment), naltrexone was just as effective as buprenorphine–naloxone in producing abstinence from illicit opioids and retaining patients in treatment.[1453,1454]

NIDA has also funded a continuing program of research demonstrating the effectiveness of initiating medication-assisted treatment for OUD in hospital EDs after hospitalization for overdose. A 2015 study found that twice as many patients were in OUD treatment at 30 days (roughly 80 percent) with ED-initiated buprenorphine and a brief negotiation interview compared with referral only or an interview and facilitated referral. When followed up, these same individuals had used less illicit opioids in the last 7 days. Studies published in 2017 have found that this intervention continues to provide benefits after 2 months and is cost effective.[1455– 1458]

NCCIH issued a FOA for research on behavioral interventions for prevention of OUD or as an adjunct to medication-assisted treatment. This effort leverages a $1 billion initiative funded by SAMHSA's State Targeted Response (STR) to the Opioid Crisis Grants, also known as the Opioid STR grants. As part of the *21st Century Cures Act*, the Opioid STR grants have been distributed to all 50 U.S. states, as well as to U.S. territories and free-associated states, to expand access to evidence-based prevention, treatment, and recovery support services; reduce unmet treatment needs; and help prevent opioid overdose deaths.[1459]

[1452] https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-19-008.html.
[1453] https://www.drugabuse.gov/about-nida/noras-blog/2018/01/nidas-past-year-achievements-point-way-toward-future-advances.
[1454] Lee JD, et al. *Lancet* 2018;391(10118):309-18. PMID: 29150198.
[1455] https://www.drugabuse.gov/news-events/news-releases/2017/02/medication-plus-ongoing-care-provided-in-emergency-departments-promising-approach-opioid-dependence.
[1456] D'Onofrio G, et al. *JAMA* 2015;313(16):1636-44. PMID: 25919527.
[1457] D'Onofrio G, et al. *J Gen Intern Med* 2017;32(6):660-6. PMID: 28194688.
[1458] Busch SH, et al. *Addiction* 2017;112(11):2002-10. PMID: 28815789.
[1459] https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-18-002.html.

NIDA has also engaged other models to develop treatments options for OUD. NIDA has partnered with small companies to develop products to help in the treatment of SUD, including the first approved FDA smartphone-based application for any health care condition granted to Pear Therapeutics The app, updated and called ReSet-O, is tailored to treat OUD by helping individuals adhere to addiction treatment and remain in treatment programs for longer. It was approved by FDA in December 2018.[1460,1461]

As part of the NIH HEAL Initiative, NIAID, NIDA, and ORIP in the NIH Office of the Director have partnered to establish a coordinated, multidisciplinary consortium, with the goal of developing opioid vaccines and testing them in clinical trials. The consortium will leverage both NIAID's extensive vaccine development programs and resources and NIDA investigators' expertise in opioid metabolism, biological transport, and mechanisms of action. To inform this effort, NIAID and NIDA hosted an October 2018 scientific agenda-setting meeting focused on immunotherapies for treatment of OUDs.[1462,1463]

Research is also active in developing treatments for addiction to other substances. NIDA's intramural research program, in collaboration with Italian researchers, reported positive findings that transcranial magnetic stimulation reduced cocaine use and cocaine cravings in patients with cocaine addiction. Follow-up studies will examine the use of this technology in treating pain and addiction to opioids and nicotine. NIDA also continues to fund investigation of existing medications that could be repurposed for addiction treatment, which would shorten the pathway to FDA approval. This includes a clinical trial for the treatment of cocaine use disorder using lorcaserin, an FDA-approved medication for obesity.[1464,1465]

Similarly, new tools have been developed that are facilitating the determination of the structure of cannabinoid and opioid receptor subtypes in different activity states.[1466,1467] This information is being used to computationally design novel analgesics that lack the adverse effects of opioids and might also be useful for treating addiction.

To encourage the development of medications to treat AUD, NIAAA founded a Clinical Investigations Group (NCIG) in 2007 to test the safety and effectiveness of promising medications in proof-of-concept Phase II clinical trials. Such studies bridge the gap between preclinical studies and large Phase III clinical trials. In FY 2016, NCIG conducted a randomized clinical trial of ABT-436, a novel compound that targets the brain's stress systems, and demonstrated that participants who received ABT-436 experienced more days of alcohol abstinence. In particular, participants who reported high levels of stress responded better to ABT-436, as evidenced by decreases in both the frequency of drinking and the number of heavy drinking

[1460] https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm576087.htm.
[1461] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628091.htm.
[1462] https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/improve-treatments-opioid-misuse-addiction.
[1463] https://grants.nih.gov/grants/guide/notice-files/NOT-AI-18-055.html.
[1464] https://www.drugabuse.gov/about-nida/noras-blog/2017/01/taking-stock-nidas-achievements-looking-to-future.
[1465] Terraneo A, et al. *Eur Neuropsychopharmacol* 2016;26(1):37-44. PMID: 26655188.
[1466] Hua T, et al. *Nature* 2017;547(7664):468-71. PMID: 28678776.
[1467] Che T, et al. *Cell* 2018;172(1-2):55-67.e15. PMID: 29307491.

days.[1468–1470] In FY 2017 and 2018, NIAAA issued several FOAs to stimulate research in these areas.[1471–1477]

An NIAAA-supported study published in 2017 evaluated the effectiveness of an individual intervention and an environmental intervention, both aimed at preventing and reducing underage drinking and its consequences among rural youth living in the Cherokee Nation in northeastern Oklahoma. The individual intervention was school-based alcohol screening and brief intervention to prevent and reduce alcohol use. The environmental intervention was a citizen-driven, community-based strategy to reduce youth access to alcohol, alcohol use, and alcohol-related consequences. The study found that students who received either or both interventions reported reduced alcohol use and heavy drinking compared with students who did not receive an intervention.[1478,1479]

In addition to research efforts, a shift in the perception of AUD as a chronic disease of the brain with potential for recovery and recurrence has helped to reduce stigma, leading to more effective interventions and facilitating the integration of prevention and treatment services into mainstream health care. In 2017, NIAAA released a new 5-year strategic plan to serve as a roadmap for optimizing the allocation of NIAAA's resources to areas of alcohol research most likely to benefit from additional support, translating scientific discoveries for the benefit of the public, and continuing to build on NIAAA's position as the nation's key source of evidence-based information on alcohol and health.[1480,1481]

In addition to developing new treatments, NIAAA continues to assist health care professionals in implementing alcohol screening and brief intervention in their practices by promoting *Helping Patients Who Drink Too Much: A Clinician's Guide for Adults*[1482] and *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide.*[1483] The *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide* assists health care providers in identifying current alcohol use and AUD in youth ages 9 to 18, as well as risk for alcohol use, especially for younger children. The *Youth Guide*, launched in 2012, provides

[1468] https://www.niaaa.nih.gov/NCIG-NIAAA-Clinical-Investigations-Group.
[1469] https://www.niaaa.nih.gov/news-events/news-releases/drug-treat-alcohol-use-disorder-shows-promise-among-drinkers-high-stress.
[1470] Ryan ML, et al. *Neuropsychopharmacology* 2017;42(5):1012-23. PMID: 27658483.
[1471] https://grants.nih.gov/grants/guide/pa-files/PAR-18-580.html.
[1472] https://grants.nih.gov/grants/guide/pa-files/PAR-18-578.html.
[1473] https://grants.nih.gov/grants/guide/pa-files/pa-18-192.html.
[1474] https://grants.nih.gov/grants/guide/pa-files/pa-18-197.html.
[1475] https://grants.nih.gov/grants/guide/pa-files/pa-18-198.html.
[1476] https://grants.nih.gov/grants/guide/pa-files/pa-17-285.html.
[1477] https://grants.nih.gov/grants/guide/pa-files/pa-17-284.html.
[1478] https://www.niaaa.nih.gov/news-events/news-releases/study-finds-effective-interventions-prevent-alcohol-use-among-american.
[1479] Komro KA, et al. *Am J Public Health* 2017;107(3):453-9. PMID: 28103073.
[1480] https://www.niaaa.nih.gov/news-events/news-releases/new-niaaa-strategic-plan-aims-advance-alcohol-research-across-broad.
[1481] https://www.niaaa.nih.gov/strategic-plan.
[1482] https://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm.
[1483] https://www.niaaa.nih.gov/publications/clinical-guides-and-manuals/alcohol-screening-and-brief-intervention-youth/.

a two-question screening tool and an innovative youth alcohol risk estimator to help clinicians overcome time constraints and other common barriers to youth alcohol screening. NIAAA-funded studies have so far validated the *Youth Guide* in pediatric ED settings, school settings, and primary care settings with racially and ethnically diverse youth, as well as among youth with chronic health conditions.[1484– 1489]

These tools are designed to help health care providers overcome barriers to alcohol screening, such as lack of familiarity with the process and time constraints. To help clinicians incorporate pharmacotherapy into their alcohol treatment practices, NIAAA partnered with SAMHSA to develop *Medication for the Treatment of Alcohol Use Disorder: A Brief Guide,*[1490] published in FY 2016. Toward this goal, NIAAA launched the Alcohol Treatment Navigator[SM] in October 2017. An online resource that offers a comprehensive strategy to help people find professionally led, evidence-based treatment for AUD,[1491,1492] it is grounded in decades of clinical and health services research. This one-of-a-kind resource outlines the features of evidence-based AUD treatment, describes the varied routes to recovery, and guides individuals through a step-by-step process for finding evidence-based care for themselves or a loved one with AUD. With the Navigator, adults searching for AUD treatment will be better able to find care that meets their unique needs, family members will feel empowered to help an adult loved one struggling with AUD, and primary care physicians and other health providers will be confident in screening their patients for AUD, knowing that they have a tool to share with their patients who need a referral to alcohol treatment. NIAAA is building on the success of the Alcohol Treatment Navigator [SM] to develop tools that help health care providers in referring their patients to AUD treatment.

Particularly vulnerable populations may also require specialized consideration for treatment. NIDA funds a program of research to develop and test interventions for SUD among individuals in justice communities. A 2016 NIDA-funded study found that initiating extended-release naltrexone in opioid-addicted prison inmates reduced their relapse rate compared to brief counseling and referral to community treatment. A later study in 2018 found that providing medication-assisted treatment for OUD after inmates were released from incarceration significantly reduced opioid-related overdoses after their release.[1493–1495]

[1484] https://www.niaaa.nih.gov/publications/clinical-guides-and-manuals/alcohol-screening-and-brief-intervention-youth/.
[1485] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-12-008.html.
[1486] D'Amico EJ, et al. *Pediatrics* 2016;138(6). PMID: 27940696.
[1487] Levy S, et al. *PLoS One* 2016;11(5):e0156240. PMID: 27227975.
[1488] Spirito A, et al. *Pediatrics* 2016;138(6). PMID: 27940674.
[1489] Tubman JG, et al. *J Sch Healt*. 2018;88(6):474-8. PMID: 29749000.
[1490] https://store.samhsa.gov/product/Medication-for-the-Treatment-of-Alcohol-Use-Disorder-A-Brief-Guide/SMA15-4907.
[1491] https://www.niaaa.nih.gov/news-events/news-releases/niaaa-alcohol-treatment-navigator-points-way-quality-treatment.
[1492] https://alcoholtreatment.niaaa.nih.gov/.
[1493] https://www.drugabuse.gov/about-nida/noras-blog/2017/01/taking-stock-nidas-achievements-looking-to-future.
[1494] Lee JD, et al. *N Engl J Med* 2016;374(13):1232-42. PMID: 27028913.
[1495] Green TC, et al. *JAMA Psychiatry* 2018;75(4):405-7. PMID: 29450443.

Through collaboration between the NIH HEAL Initiative and NIDA, the Justice Community Opioid Innovation Network (JCOIN) is studying the effectiveness and adoption of addiction treatment medications, interventions, and technologies in criminal justice settings to improve the quality of OUD treatment. JCOIN facilitates partnerships between local and state justice systems and community-based treatment providers to generate real-world evidence to address the unique needs of individual with OUD in justice-involved populations and identify which strategies are most effective.[1496– 1499]

Among pregnant women with OUD, more frequent doses of buprenorphine may be needed because pregnancy can significantly change the way the human body processes medications. It follows that dosing for pregnant women may differ from dosing for non-pregnant women. NICHD-supported researchers reported that pregnant women being treated with buprenorphine for opioid dependence need more frequent daily doses (three to four times daily) of the medicine than the currently recommended dosing for non-pregnant patients (once or twice daily). Because a pregnant woman's body clears the drug more rapidly, the standard dosing for non-pregnant women does not produce sufficient blood concentration of buprenorphine in pregnant women to prevent opioid withdrawal syndrome.[1500] Recognizing the need and in response to an NICHD workshop in 2016, NICHD issued a FOA calling for research to address treatment of pregnant women with OUD, including pharmacokinetic and pharmacodynamic studies of medications used for maternal treatment.[1501]

This area is of particular importance because the type of treatment received by pregnant mothers also affects the health of their children. NICHD-supported researchers analyzed a large dataset of electronic pharmacy records and compared women treated with methadone with women treated with buprenorphine. Those treated with methadone had more prenatal care visits, a higher chance of delivering vaginally, and a lower risk of testing positive for illicit drugs after treatment began. Beyond considering the impact of treatment selection on children, these results underscore the complexity of selecting the most appropriate medication given a patient's disease severity, mental health, and recovery resources.[1502]

In a study supported by NICHD, researchers studied placental cells gathered using a procedure routinely used to test for birth defects in the first trimester to determine whether the death of cells in the placenta resulting from increased levels of calcium that occurs as a result of exposure to alcohol could be prevented. Researchers divided these cells into three groups: One group was exposed to alcohol; another group was pretreated with nifedipine, a calcium channel blocker, before being exposed to alcohol; and a third group was not exposed to either alcohol or nifedipine. Cells exposed to only alcohol died, as expected. Cells pretreated with nifedipine did not die after alcohol exposure; nifedipine has been used

[1496] https://www.drugabuse.gov/drugs-abuse/opioids/nih-heal-initiative/justice-community-opioid-innovation-network-jcoin.
[1497] https://grants.nih.gov/grants/guide/rfa-files/rfa-da-19-025.html.
[1498] https://grants.nih.gov/grants/guide/rfa-files/rfa-da-19-024.html.
[1499] https://grants.nih.gov/grants/guide/rfa-files/rfa-da-19-023.html.
[1500] Bastian JR, et al. *Am J Obstet Gynecol* 2017;216(1):64.e1-64.e7. PMID: 27687214.
[1501] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-18-036.html.
[1502] Lemon LS, et al. *Epidemiology* 2018;29(2):261-8. PMID: 29112519.

safely during pregnancy in the past. Clinical studies are needed to confirm these results, but they raise the possibility that calcium channel blockers could help protect placental cells from some toxic effects of alcohol.[1503]

Prevention

An alternative strategy to reduce SUD is to prevent use and misuse to begin with. NIDA funds a SUD prevention program called Communities That Care (CTC), a collaborative, multipronged prevention strategy customized to the needs of individual communities. Studies of the CTC system in 24 communities found that adolescents who participated showed significant, sustained reductions in initiation of risky behaviors, including substance use. Recently, a 2018 study found that implementation of CTC during adolescence increased the likelihood of sustained abstinence from alcohol, tobacco, or marijuana use by 49 percent and antisocial behavior by 18 percent, and reduced lifetime incidence of violence by 11 percent through age 21.[1504]

In FYs 2016–2018, NIAAA continued to promote the College Alcohol Intervention Matrix (CollegeAIM) launched in 2015, an easy-to-use tool to help college and university officials identify and compare evidence-based alcohol interventions appropriate for their campuses. CollegeAIM rates nearly 60 different individual- and environmental-level alcohol interventions, evaluating their cost, effectiveness, and ease of implementation.[1505]

Strategies for prevention of OUD is multipronged and includes reducing the prescription of opioids to begin with, finding and developing pain medication alternatives to opioids, and raising awareness about its risks among the general population.

Under the leadership of the NIH HEAL Initiative—and with contributions from NCATS, NCCIH, NCI, NEI, NIA, NIAAA, NIAMS, NICHD, NIDCR, and NINDS—Pragmatic and Implementation Studies for the Management of Pain (PRISM) supports studies to integrate evidence-based interventions for pain into health care systems or implement health care systems changes to improve adherence and uptake to pain management guidelines. Studies will be embedded in real-world settings to determine the effectiveness of multiple interventions across pain conditions.[1506]

To emphasize the essential role of the oral health community in addressing the opioid overdose epidemic, NIDCR leadership coauthored a perspective that outlines research efforts to inform clinical decision making related to opioid prescribing practices.[1507] An NIDCR-supported deimplementation grant is testing non-opioid pain management strategies like NSAIDs or acetaminophen following dental extractions. The researchers are testing a new clinical decision-making tool to provide dentists with recommendations for non-opioid pain prescriptions. This tool could help dentists tailor pain management strategies for each

[1503] Bolnick AD, et al. *Alcohol Clin Exp Res* 2018;42(1):53-60. PMID: 29048755.
[1504] Oesterle S, et al. *Am J Public Health* 2018;108(5):659-65. PMID: 29565666.
[1505] https://www.collegedrinkingprevention.gov/CollegeAIM.
[1506] https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-19-004.html.
[1507] Somerman MJ, et al. *J Am Dent Asso.* 2018;149(8):663-5. PMID: 30055662.

patient and substantially reduce the number of post-treatment opioid prescriptions given to patients.[1508] NIDCR's National Dental Practice–Based Research Network aims to answer questions of everyday relevance to dental practitioners and their patients. One of its studies is addressing the nationwide opioid overdose crisis, and its findings suggest that prescription drug monitoring programs and patient education may lower the risk of subsequent opioid misuse.[1509]

Early Phase Preclinical Investigation Network (EPPIC Net) provides a robust and readily accessible infrastructure to support rapid design and performance of high-quality Phase II clinical trials to test promising novel therapeutics for pain. Led by NINDS through support from the NIH HEAL Initiative, exploratory clinical trials may include characterization and biomarker studies in patients who have selected pain conditions, including well-defined conditions with high unmet therapeutic needs across the lifespan.[1510]

NIDA leads the annual National Drug and Alcohol Facts Week, co-sponsored with NIAAA, which involves more than 2,000 local events across the nation and around the world. As part of this week, NIDA hosts National Drug and Alcohol Facts Chat Day, an annual 10-hour live web-based event involving thousands of teens from all over the country.[1511]

Population and Policy

Many treatment and prevention interventions that can be applied to individuals also have a complementary population or policy-level implementation as well. NIH-funded research has pointed to the need to apply population-level interventions to address SUD across the spectrum of substances.

NIH-supported researchers are aiming to establish tobacco control models in LMICs. The models developed will incorporate local talent, resources, and government public health agencies in interventions across the countries of Georgia and Armenia.[1512]

NIDA partnered with the Appalachian Regional Commission, CDC, and SAMHSA to issue nine grants to help communities develop comprehensive approaches to prevent and treat consequences of opioid injection, including SUD, overdose, HIV infection, hepatitis B and C virus infections, and sexually transmitted infections. Funded in FY 2017, these projects will work with state and local communities to develop best-practice responses that can be implemented by public health systems in the nation's rural regions.[1513,1514]

[1508] https://projectreporter.nih.gov/project_info_description.cfm?aid=9548193&icde=35994252.
[1509] McCauley JL, et al. *J Am Dent Assoc* 2018;149(5):353-62. PMID: 29550022.
[1510] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-19-023.html.
[1511] https://teens.drugabuse.gov/national-drug-alcohol-facts-week.
[1512] http://news.emory.edu/stories/2017/09/NIH_tobacco_control/index.html.
[1513] https://www.drugabuse.gov/news-events/news-releases/2017/08/grants-awarded-to-address-opioid-crisis-in-rural-regions.
[1514] https://www.drugabuse.gov/news-events/news-releases/2016/02/nida-arc-announce-funding-opportunity-research-projects-to-address-opioid-injection-use-its.

In FY 2016, NIAAA expanded its Alcohol Policy Information System (APIS), a database that tracks alcohol-related state and federal policies, to include state-level policies on the recreational use of marijuana. Designed primarily as a tool for researchers, APIS is intended to encourage and facilitate research on the effects and effectiveness of alcohol- and marijuana-related policies.[1515]

Transplantation

Since the first successful kidney transplant was performed between identical twins in 1954, transplantation has become the treatment of choice for end-stage organ failure. In the U.S., the most commonly transplanted organs are the kidney, liver, heart, lungs, pancreas, and intestines.[1516] On any given day, approximately 75,000 people are on the active waiting list for organs, but only around 8,000 deceased organ donors are available each year, with each providing on average 3.5 organs.[1517] Despite tremendous progress, however, major barriers still remain to the overall success of transplantation, which include immunological incompatibility between donor and recipient, acute rejection, chronic graft dysfunction, and complications from requisite long-term use of immunosuppressive drugs. NIH supports basic and clinical research that focuses on the immunologic processes underlying transplant rejection and acceptance; ways to reduce or eliminate the need for immunosuppressive drugs; and the development of new, less toxic antirejection therapies.

In June 2017, the NHLBI and American Association for Thoracic Surgery co-sponsored a workshop designed to bring participants together to summarize the current state of the science in adult lung transplantation, identify knowledge gaps, and determine priorities in clinical lung transplant research that could be addressed in the near future. A workshop report was published in 2018 that will help guide the research agenda.[1518]

An observational study of heart transplant recipients supported by NINR found that men were older, more ill, and more likely to receive a heart transplant than women, who were often treated less aggressively for their heart failure.[1519] Women were also more likely to be hospitalized for acute rejection and more likely to experience moderate or severe rejections. A compelling need exists for future research to examine why these clinical and gender differences persist.

NHLBI supports research to improve bone marrow transplantation for sickle cell disease. Currently, bone marrow transplantation is the only accessible cure for the disease, but, in general, it is effective only for patients who have an immunologically matched donor, which greatly limits its use.[1520] To make bone marrow transplants more widely available, NHLBI intramural researchers have developed a new protocol and are testing it in a clinical trial; known as a haploidentical transplantation, this protocol involves

[1515] https://alcoholpolicy.niaaa.nih.gov/.
[1516] https://www.cdc.gov/transplantsafety/overview/key-facts.html.
[1517] https://www.cdc.gov/transplantsafety/overview/key-facts.html#:~:text=In%20the%20United%20States%2C%20the,providing%20on%20average%203.5%20organs.
[1518] Mulligan MS, et al. *J Thorac Cardiovasc Surg* 2018;156(6):2355-65. PMID: 30244865.
[1519] Hickey KT, et al. *Eur J Cardiovasc Nurs* 2017;16(3):222-29. PMID: 27189203.
[1520] Bauer DE, et al. *Blood Cells Mol Dis* 2017;67:155-68. PMID: 28893518.

obtaining bone marrow from a parent, child, or sibling of the patient who is a partial immunological match, with other adjustments made to help prevent immune rejection of the donated marrow.[1521]

In a first-in-human study, NHLBI-funded researchers tested whether a molecule known as growth-regulated oncogene beta—or a combination of growth-regulated oncogene beta and granulocyte colony-stimulating factor—could release blood-forming stem cells from bone marrow more efficiently, with less pain.[1522] They found that the combination mobilized highly engraftable stem cells with a single injection and was generally well tolerated. This next-generation strategy could increase the bone marrow donor pool and, thus, expand the availability of bone marrow transplants for more patients with a variety of blood disorders. This approach also could provide a safer, less painful method to isolate a patient's own blood stem cells for use in genetic therapies.

Clinical trial findings reported in January 2018 showed that a therapeutic regimen involving transplantation of a person's own blood-forming stem cells improves survival and quality of life for people with severe scleroderma, a life-threatening autoimmune disease.[1523] The regimen, known as myeloablative autologous hematopoietic stem cell transplant, includes chemotherapy and total-body radiation to destroy the bone marrow, followed by transplantation of the person's own blood-forming stem cells to reconstitute the marrow and immune system.[1524] The NIAID-funded study found the regimen to be superior to treatment with the immune-suppressing drug cyclophosphamide.[1525]

Lymph is a colorless fluid comprising white blood cells that bathes tissues and then drains back to the blood through vessels similar to blood vessels. The lymphatic system is involved in transplanted tissue rejection, as well as cancer and infectious disease responses. When the cornea—the transparent front of the eye—becomes damaged by disease or injury, ophthalmologists may perform a cornea transplant to restore vision to the recipient patient. As with other organ transplant procedures, recipient patients may reject the transplanted tissue. NEI-funded researchers discovered a new growth factor for the formation of new lymph vessels called galectin-8.[1526] They found that mice lacking galectin-8 had much lower rates of corneal transplant rejection and were more resistant to ocular herpes simplex virus infection, suggesting galectin-8 is a candidate therapeutic target. These findings may extend to non-eye organ transplant rejection and cancer metastasis.

[1521] https://www.nhlbi.nih.gov/news/2016/skys-limit-woman-sickle-cell-disease-gets-life-changing-bone-marrow-transplant.
[1522] Hoggatt J, et al. *Cell* 2018;172(1-2):191-204.e10. PMID: 29224778.
[1523] https://www.niaid.nih.gov/news-events/stem-cell-transplant-severe-scleroderma-improves-survival-quality-life.
[1524] https://clinicaltrials.gov/ct2/show/study/NCT00114530.
[1525] Sullivan KM, et al. *N Engl J Med* 2018;378(1):35-47. PMID: 29298160.
[1526] Chen WS, et al. *Nat Commun* 2016;7:11302. PMID: 27066737.

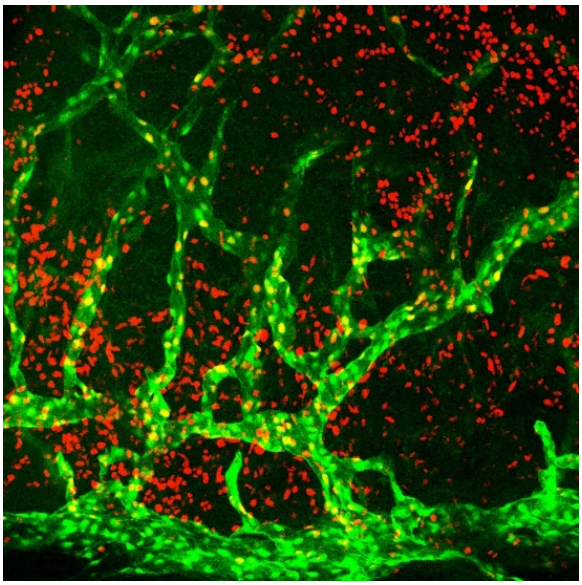

Figure 79. Galectin-8 promotes corneal lymphangiogenesis in mice. This photo was chosen as a winner of the 2016 NIH-funded research image call. Credit: Drs. Wei-Sheng Chen and Noorjahan Panjwani. Department of Ophthalmology, Tufts University, Boston, MA, U.S.A.

NEI intramural researchers are poised to launch the first clinical trial using human tissue created from patient-derived iPSCs. iPSCs are made by genetically reprogramming adults cells so that they can be converted into any cell type in the body, a breakthrough recognized with the 2012 Nobel Prize for Medicine. The trial will test a treatment for geographic atrophy, an advance form of age-related macular degeneration, characterized by the death of retinal pigment epithelium (RPE) cells and, subsequently, the light-detecting retinal neurons dependent on RPE. After years of in-depth characterization of RPE and research uncovering key steps in RPE development, NEI researchers have developed current good manufacturing practices for the production of RPE iPSCs to be used in human patients for cell therapy.[1527] Key preclinical studies in rodents and pigs have demonstrated that not only are these human cells safe, but they also successfully rescue lost vision in models of macular degeneration.

Another team of NEI-funded clinical researchers have focused on an adult stem cell type ripe for clinical trials.[1528] They are working on cultivating corneal limbal cells, which are responsible for renewing the front layer of the transparent cornea. In thousands of patients with limbal stem cell deficiency, the loss of these cells causes visual impairment from chronic inflammation, abnormal blood vessel growth, and opaque corneas. This NEI project is supported by the *21st Century Cures Act* Regenerative Medicine Program.

People with type 1 diabetes who have impaired awareness of hypoglycemia—an inability to sense low blood sugar levels—are at high risk for experiencing dangerous drops in blood sugar (known as severe hypoglycemia) that can lead to seizures, loss of consciousness, and death. In 2016, researchers from the

[1527] Sharma R, et al. *Sci Transl Med* 2019;11(475). pii: eaat5580. PMID: 30651323.
[1528] https://clinicaltrials.gov/ct2/show/NCT02592330.

NIH-funded Clinical Islet Transplantation Consortium[1529] reported results from a clinical trial[1530] showing the benefits of transplantation of pancreatic islets (cell clusters that contain insulin-producing cells) for people with type 1 diabetes complicated by severe hypoglycemia despite expert medical treatment.[1531,1532] The 48 participants each received at least one transplant of pancreatic islets prepared from deceased donors. After two years of transplantation, 71 percent of participants were free of severe hypoglycemic events, had near-normal control of blood sugar levels, and had restored hypoglycemic awareness. The researchers are continuing to monitor the patients to assess the durability of the benefits of islet transplantation and long-term risks of chronic immunosuppression. Patients who took part in the study also reported improved diabetes-related quality of life.[1533]

Urologic and Gynecologic Diseases and Conditions

Diseases and conditions affecting the bladder and associated structures of the lower urinary tract affect people of all ages, result in significant health care expenditures, and may lead to substantial disability and impaired quality of life. For example, according to national public health surveys conducted over several years, 1 in 10 U.S. adults 18 years of age and older are estimated to suffer from daily urinary incontinence, and most of those affected are women.[1534] Gynecologic condition—such as uterine fibroids, endometriosis, adenomyosis, ovarian cysts, and menstrual disorders—account for a significant amount of suffering among women across the U.S. Endometriosis, for example, affects about 10 percent of women of reproductive age and contributes significantly to the development of pelvic adhesions, infertility, ectopic pregnancy, and chronic pelvic pain.[1535] Spearheaded by NICHD and NIDDK, NIH supports all areas of research to help improve the health of those suffering from urologic and gynecologic diseases and conditions, conducting investigations into the epidemiology, natural history, etiology, basic mechanisms, prevention, diagnosis, and treatment of these diseases.

Understanding Prevalence, Risk Factors, and Underlying Biology

Affecting between 5 and 10 percent of women ages 18–44 years, polycystic ovary syndrome (PCOS) is a condition in which the ovaries contain numerous small, cyst-like sacs. Along with infertility, symptoms may include obesity; irregular, missing, or prolonged menstrual periods; excessive facial and body hair; and insulin resistance, a prediabetic condition in which higher-than-normal amounts of insulin are produced to maintain normal blood glucose levels. Researchers supported by NICHD have discovered that women with PCOS may accumulate fat around the internal organs of the abdomen but are less likely to

[1529] https://www.citisletstudy.org/.
[1530] https://clinicaltrials.gov/ct2/show/NCT00434811.
[1531] Hering BJ, et al. *Diabetes Care* 2016;39(7):1230-40. PMID: 27208344.
[1532] https://www.niaid.nih.gov/news-events/islet-transplantation-restores-blood-sugar-awareness-and-control-type-1-diabetes.
[1533] https://www.niaid.nih.gov/news-events/islet-transplantation-improves-quality-life-people-hard-control-type-1-diabetes.
[1534] https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/urologic-diseases-in-america.
[1535] https://www.nichd.nih.gov/health/topics/endometri/conditioninfo.

store fat beneath the skin surrounding the abdomen, backside, and thighs, compared with women who do not have the condition.[1536] The patients with PCOS all had high androgen levels, which the researchers believe could have influenced how they store fat and how their fat cells function. According to the researchers, this altered pattern of fat storage may account for the higher risk for diabetes and heart disease frequently seen in women who have PCOS. In the study, women with the condition used insulin less efficiently than other women and tended to have higher levels of the blood fats and cholesterol types that have been linked to heart disease.

Compared with White women, Black women are more likely to be diagnosed with fibroids at a younger age and to have more and larger fibroids. NICHD-supported researchers conducted a mutation analysis of *MED12*, a gene that is mutated in approximately 70 percent of fibroids in Black women undergoing fibroid surgery.[1537] Although *MED12* was associated with tumorigenesis, mutation analyses did not provide conclusive evidence that genetic anomalies found by the researchers are responsible for racial differences in the onset or severity of uterine fibroids in Black women.

NIDDK-supported researchers have studied changes that occur in the bladder and invading bacteria that affect both acute and recurrent infection with uropathogenic *Escherichia coli* (UPEC). Findings from a study in an animal model suggest that a history of urinary tract infection (UTI) and whether it resolves or becomes chronic could have an important impact on susceptibility to future infection and that this variance in susceptibility may be due in large part to how the bladder tissue itself reacts to an initial infection.[1538] Another NIDDK-supported study focused on pili—surface molecules with sticky tips, or adhesins, that are part of how UPEC attain entry into bladder cells—and found that UPEC deliver a one-two punch, using one pilus to enable initial attachment but then deploying a second pilus that adheres to inflamed bladder tissue, providing an advantage in establishing chronic infection in mice.[1539] Vaccination against the adhesin on the second pilus protected mice from infection progression, suggesting this approach could be a viable therapeutic target.

Microbes need metals like iron and copper to survive and, and during infection, the microbes and host compete for these metals, limiting their availability. Researchers have now found evidence suggesting that UPEC use a small iron-scavenging molecule (siderophore) called yersiniabactin (Ybt) more broadly, to also modulate the uptake of copper, increasing the importance of Ybt to UPEC.[1540] Encouragingly, a research team has shown that vaccinating mice with Ybt or another siderophore (aerobactin) reduces acute bacterial burden in the mouse bladder by 12- and 19-fold, respectively.[1541] On the other hand, another research team has isolated a set of novel molecules from non-*E. coli* bacteria, including a molecule called nicoyamycin A, that show promise as inhibitors of UPEC growth under low-iron conditions.[1542]

[1536] https://www.nichd.nih.gov/news/releases/Pages/110316-PCOS.aspx.
[1537] Hayden MA, et al. *Cancer Genet* 2018;222-223:1-8. PMID: 29666002.
[1538] O'Brien VP, et al. *Nat Microbiol* 2016;2:16196. PMID: 27798558.
[1539] Conover MS, et al. *Cell Host Microbe* 2016;20(4):482-92. PMID: 27667696.
[1540] Koh EI, et al. *Nat Chem Bio.* 2017;13(9):1016-21. PMID: 28759019.
[1541] Mike LA, et al. *Proc Natl Acad Sci USA* 2016;113(47):13468-73. PMID: 27821778.
[1542] Mike LA, et al. *Chem Commun* 2017;53(95):12778-81. PMID: 29139494.

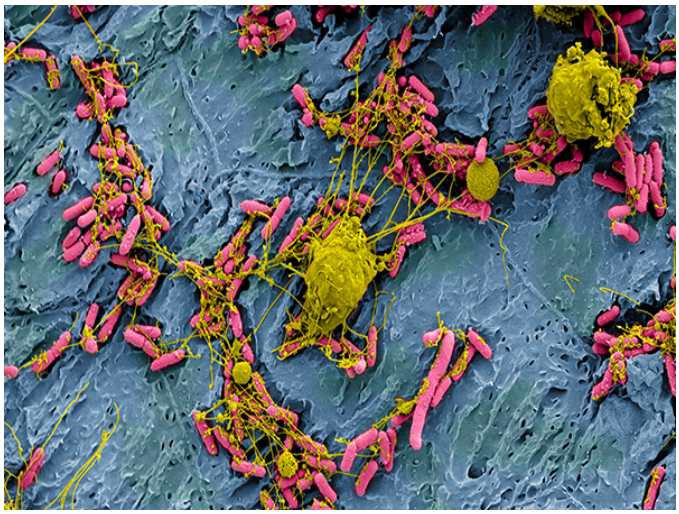

Figure 80. Scanning electron microscope image of the bladder (blue) of a laboratory mouse that was infected with the bacterium *E. coli* (pink), a common cause of urinary tract infections. White blood cells (yellow) reach out with what appear to be stringy extracellular traps to immobilize and kill the bacteria. Credit: Valerie O'Brien, Matthew Joens, Scott J. Hultgren, James A.J. Fitzpatrick, Washington University in St. Louis.

Improving Treatment and Prevention

The NIDDK-supported Lower Urinary Tract Dysfunction Research Network (LURN) was established to better define clinical phenotypes, better describe the impact and diversity of symptoms, and develop new patient-centric tools for improved measurement of clinical symptoms, all with the goals of informing future clinical studies and improving patient care.[1543] In the second 5-year funding cycle, LURN investigators will continue subtyping participants with lower urinary tract symptoms (LUTS), with the expectation that clinically useful patient subtypes will be identified.[1544] Research efforts will include both continued analysis of data from the initial LURN results and the development of additional new and novel collaborative studies to further improve our understanding of lower urinary tract (LUT) dysfunction. One LURN study of 510 female participants found that although the majority reported having urinary incontinence (UI), increasing UI severity rather than the presence or type of urinary incontinence was associated with increased depression, anxiety, and stress.[1545] Another study in this same group found that women with UI reported significantly worse constipation, diarrhea, fecal incontinence, and sexual function compared with women without UI.[1546,1547]

LUT symptoms are those associated with any type of LUT dysfunction or conditions (e.g., urinary incontinence, UTIs), as well as those with as-yet unidentified cause. LUT symptoms—which can include

[1543] https://nih-lurn.org/.
[1544] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-510.html.
[1545] Cameron AP, et al. *Neurourol Urodyn* 2018;37(8):2586-96. PMID: 29635702.
[1546] Andreev VP, et al. *J Urol* 2018;200(6):1323-31. PMID: 29990467.
[1547] Siddiqui NY, et al. *J Urol* 2018;200(4):848-55. PMID: 29730202.

frequent or urgent urination, the need to urinate multiple times throughout the night, and problems with voiding—and their associated conditions not only have a direct negative impact on health but also exacerbate or contribute to other chronic health problems in women, including obesity, diabetes, and depression. The NIDDK-supported, multicenter, multidisciplinary Prevention of Lower Urinary Tract Symptoms Research Consortium is pursuing qualitative and quantitative research studies needed to establish the scientific basis for future prevention-intervention research targeting LUT symptoms and conditions in women and girls.[1548] The Consortium has developed and published a novel, multifaceted research definition of bladder health that can inform approaches for evaluation of bladder health promotion and prevention of LUT symptoms—both in research and in public health initiatives. The Consortium also conducted a review and meta-analysis of more than nearly 30 years of published studies[1549] that elucidated a profound gap in the ability to evaluate LUT symptoms by occupation types, indicating that future studies should characterize voiding frequency and toilet access in a consistent manner by occupation, as well as explore its relation to LUTS development.[1550,1551]

The NIDDK-supported *How to Help Men with LUTS Help Themselves* meeting addressed the need to enhance the ability to engage in and maintain behavioral interventions for secondary prevention strategies in men with LUTS.[1552] LUTS in men is extremely common and usually is associated with an enlarged prostate. Although many examples in other fields of medicine exist, literature on methods for behavioral interventions for LUTS in men is lacking, and even less literature is available on specific self-management skills, such as goal setting, self-monitoring, and problem solving. The meeting objectives were to review the evidence on various factors affecting LUTS in men, discuss the knowledge base for self-management of LUTS in men, and identify potential intervention strategies to reduce the impact of LUTS on men's quality of life.

In women with endometriosis, the endometrial tissue that normally lines the uterus also grows outside the uterus, typically on organs in the lower abdomen or pelvic cavity. Existing treatment options for endometriosis—such as anti-inflammatory medications, hormonal treatment, and various surgical approaches—all have significant drawbacks. Researchers found that bufalin (a naturally occurring component in certain Chinese traditional medicines) disrupted a key protein in endometriosis called steroid receptor coactivator, which reduced the proliferation of connective tissue cells in endometrial lesions in experimental mice.[1553] In laboratory experiments, scientists showed that this compound suppressed the growth of certain human endometrial cells isolated from patients with endometriosis. This study shows that compounds like bufalin that inhibit the function of steroid receptor coactivators may comprise a potential new class of drugs to treat endometriosis.

[1548] https://plusconsortium.umn.edu/.
[1549] Markland A, et al. *Neurourol Urodyn* 2018;37(8):2881-92. PMID: 30272814.
[1550] Brady SS, et al. *Neurourol Urodyn* 2018;37(8):2951-64. PMID: 30136299.
[1551] Lukacz ES, et al. *J Womens Health (Larchmt)* 2018;27(8):974-81. PMID: 29792542.
[1552] https://www.niddk.nih.gov/news/meetings-workshops/2016/how-to-help-men-with-luts-help-themselves.
[1553] Cho YJ, et al. *J Endocrinol* 2018;237(3):255-69. PMID: 29636364.

In two studies supported by NICHD, researchers found that overweight and obese women with PCOS may have a greater chance of becoming pregnant if they lose weight before beginning fertility treatment.[1554] In one of the analyzed studies, 187 obese and overweight women with PCOS were immediately treated with clomiphene, a drug that induces ovulation. In the other study, 142 women with PCOS began a weight-loss program consisting of lower caloric intake, exercise, and anti-obesity medication before starting clomiphene treatment. Women who were treated with clomiphene alone had an ovulation rate of 44.7 percent and a live birth rate of 10.2 percent. The women who received clomiphene after the weight-loss program had a 62 percent ovulation rate and a 25 percent live birth rate.

Uterine fibroids are noncancerous tumors that develop from the muscular layer of the uterus, and affect up to 70 percent of U.S. women at some point in their lifetimes. Although many fibroids do not cause symptoms, others can cause heavy menstrual bleeding, pain, infertility, and other symptoms. Fibroids are often treated with hysterectomy (removal of the uterus), but many women prefer less invasive treatments. Scientists compared two minimally invasive fibroid treatments: uterine artery embolization (UAE) and MRI-guided focused ultrasound surgery (MRgFUS). Women undergoing UAE reported having more post-procedure pain, using more prescription medications, having longer recovery times, and taking longer to return to work and normal activity than women in the MRgFUS group.[1555] However, the UAE group's treatment time was shorter and was all performed in one day. By contrast, women in the MRgFUS group had a longer procedure time, with 53 percent requiring two days to complete the treatment. This study is the first clinical trial to compare these treatments. The results can help to shape recommendations for fibroid treatment.

Analyzing records of more than 190,000 women enrolled in one of the largest U.S. commercial health plans, NICHD-supported researchers found that for women with uterine fibroids, cholesterol-lowering drugs known as statins reduced fibroid-related symptoms and the number of surgeries. The scientists emphasized that their study focused only on women whose elevated blood cholesterol levels prompted their treatment with statins and that it would be important to study whether statins could help women with fibroids who do not also have elevated blood cholesterol.

Vaginal prolapse occurs when pelvic organs bulge into the vagina or protrude beyond the opening of the vagina, causing discomfort or even difficulty emptying the bladder or bowels. Vaginal prolapse is one of several pelvic floor disorders in which muscles or connective tissues that help support pelvic orders (bladder, bowel, uterus) become weakened or injured. NICHD supported a 5-year comparison of two surgeries for vaginal prolapse—uterosacral ligament suspension and sacrospinous ligament fixation—which found no significant differences in success rates between the two.[1556] The study also showed that most women who underwent either surgery reported improvements in their symptoms. Furthermore, researchers found no differences in recurrence rates or symptoms among women who received physical therapy to improve muscle control, compared with those who did not receive physical therapy.

[1554] Legro RS, et al. *J Clin Endocrinol Metab* 2016;101(7):2658-66. PMID: 27172435.
[1555] Barnard EP, et al. *Am J Obstet Gynecol* 2017;216(5):500.e1-11. PMID: 28063909.
[1556] Jelovsek JE, et al. *JAMA* 2018;319(15):1554-65. PMID: 29677302.

Pregnancy and childbirth are among the factors that increase a woman's risk of developing urinary incontinence. If initial treatments with pelvic floor muscle training and/or medication are unsuccessful, physicians may recommend surgery or a series of Botox injections. Until a recent RCT, however, little evidence was available on which treatment was more effective. With the support of NICHD, the trial found that the injections were somewhat more effective than surgery in reducing episodes of urinary incontinence, although they also posed a higher risk of UTI.[1557] These findings are expected to help women and their physicians choose a treatment that is best for their individual situations.

An NICHD-supported study on urgency urinary incontinence reported the effect of age on treatment outcomes.[1558] The researchers examined 6-month outcomes of a clinical trial that evaluated treatment with botulinum toxin or a type of pacemaker that sends electrical signals to control the bladder. The team found that women in the trial had improved symptoms and quality of life regardless of age or treatment type. They also discovered that women under 65 years of age had greater achievement of continence and symptom improvement with LUT infections. The results should encourage women, regardless of age, to seek treatment for urinary incontinence.

NIDDK held a series of two meetings in 2017 and 2018 with an overarching goal to develop fundable, interdisciplinary, investigator-initiated research proposals that will lead to better outcomes for currently available treatments by individualizing them to each patient and considering characteristics across the spectrum from biology to the social determinants of health. The first meeting on *Individualizing Treatment—Broadening the Framework for Urinary Incontinence Research* set the stage on the status of existing treatments and the factors that might predict treatment success.[1559] The second meeting on *Individualizing Treatment for Urinary Incontinence—Evolving Research Questions into Research Plans* sought to build upon ideas generated in the first meeting to facilitate development of viable research proposals.[1560]

An NIDDK-supported, multicomponent strategy to reduce catheter-associated UTIs was tested in 404 community-based nursing homes in 38 states.[1561] The strategy included training in aseptic (germ-free) insertion of catheters, catheter care and incontinence care planning, and catheter removal. The multipronged strategy did not reduce the frequency of catheter use, yet it succeeded in decreasing UTI rates by 54 percent, compared with the infection rate at the same facilities before the study began.

[1557] Amundsen CL, et al. *JAMA* 2016;316(13):1366-74. PMID: 27701661.
[1558] Komesu YM, et al. *Am J Obstet Gynecol.* 2018;218(1):111.e1-9. PMID: 29031894.
[1559] https://www.niddk.nih.gov/news/meetings-workshops/2017/individualizing-treatment-broadening-the-framework-for-urinary-incontinence-research.
[1560] https://www.niddk.nih.gov/news/meetings-workshops/2018/individualizing-treatment-urinary-incontinence-evolving-research-questions-research-plans-2017.
[1561] Mody L, et al. *JAMA Intern Med* 2017;177(8):1154-62. PMID: 28525923.

Autoimmune Diseases

Affecting more than 23.5 million people, autoimmune diseases are among the most prevalent diseases in the U.S.[1562] Autoimmune diseases are a group of more than 80 chronic and often rare illnesses that result when the body's immune system attacks healthy cells. They can affect anyone and almost any part of the body. Systemic lupus erythematosus (lupus), MS, type 1 diabetes, rheumatoid arthritis (RA), and inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, rank among the most common—and well known—autoimmune diseases. More information about NIH research on MS and diabetes is available in other sections of this chapter. The causes of autoimmune diseases remain largely unknown, with diagnosis sometimes taking years. Cures have yet to be discovered, and patients often face a lifetime of illness and treatments. The chronic and debilitating nature of these diseases can be a substantial financial and social burden to the patients, their families, and their communities.

Summary of NIH Activities

NIH is committed to advancing the understanding of how autoimmune diseases develop and to applying these results to improve the health and quality of life of patients affected with these diseases. To assist in priority setting related to autoimmune disorders, NIH has, in the case of some disorders, developed strategic plans to guide research in the field. For example, in response to a request from the Congressional Lupus Caucus, NIAMS led the development of the NIH Action Plan for Lupus Research. The plan was developed collaboratively among the NIH ICs with an interest and investment in lupus research, with extensive input from the broader community of researchers, health care providers, patients, and the Lupus Federal Working Group.[1563] The plan represents a synthesis of internal and external input on promising future research directions to improve the lives of people with lupus. The plan also highlights many opportunities to better understand lupus at the molecular, individual, and population levels. Topics include research needs related to disease etiology, mechanisms, treatments, diagnostic approaches, and health services, as well as workforce issues and opportunities for partnerships.[1564]

NIH supports research on the underlying molecular basis and screening, diagnosis, and treatment of autoimmune diseases, as well as on identifying emerging autoimmune diseases. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH ICOs—including NCATS, NCI, NHGRI, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NIEHS, NIGMS, NIMHD, NINDS, and ORWH—conduct and support autoimmune disease research. NIH funding for autoimmune diseases research was $883 million in FY 2016, $934 million in FY 2017, and $888 million in FY 2018.[1565]

[1562] https://www.niehs.nih.gov/health/topics/conditions/autoimmune/index.cfm.
[1563] https://www.niams.nih.gov/newsroom/announcements/nih-announces-action-plan-lupus-research.
[1564] https://www.niams.nih.gov/about/working-groups/lupus-federal/action-plan.
[1565] https://report.nih.gov/categorical_spending.aspx.

Understanding the Biology

Understanding the biological factors underlying autoimmune disease may lead to developing new and more effective treatments for patients. NIH-supported research has led to a greater understanding of antigen presentation, immune responses, genetic factors, the role of cell death, risk factors for autoimmune disease, and non-immune responses contributing to autoimmunity.

An overactive immune system can lead to autoimmune diseases, suggesting that understanding the immune system dysfunction may provide insight into developing new autoimmune disease treatments. For example, a study using cutting-edge epigenetic approaches to investigate fibroblast-like synoviocytes (FLS)—a type of cell that lines joints and contributes to joint destruction in RA—enabled researchers to uncover RA-specific pathways and transcription factors. Unexpectedly, they discovered that a signaling pathway associated with Huntington's disease, a fatal genetic brain disease, ranked top among RA pathways—above the many pathways already known to be relevant to the disease.[1566] They also showed that a protein involved in Huntington's disease is present in RA FLS and plays a role in these cells' invasion into cartilage. This startling overlap with Huntington's disease suggests the possibility of new therapeutic targets and drugs for both conditions.

In another study, funded in part by NIAID and NIAMS, researchers found that DNA methylation patterns differed between FLS obtained from the knees versus the hips of RA patients.[1567] These findings suggest that RA mechanisms may vary by joint and may help explain why some joints improve, while others do not, in response to the same drug treatment.[1568] It also highlights the need for further research to determine how differences between FLS from various joints affect clinical outcomes and therapeutic responses.

NIDCR-supported researchers discovered that the periodontal pathogen *Aggregatibacter actinomycetemcomitans* (Aa) may be an environmental trigger of autoimmunity in RA. They found that Aa can cause a post-translational protein modification linked to RA, called citrullination, which was also found in gum tissue of individuals with periodontal disease, suggesting the process of citrullination may be a common connection between the two diseases. In RA, citrullinated proteins accumulate and trigger release of destructive antibodies that attack and induce painful inflammation in the joint. Study participants with RA were much more likely to have an Aa infection, establishing another connection between Aa and RA.[1569]

[1566] Ai R, et al. *Nat Commun* 2018; 9(1):1921. PMID: 29765031.
[1567] https://www.niams.nih.gov/newsroom/spotlight-on-research/rheumatoid-arthritis-joint-specific-cell-differences-suggest-need.
[1568] Ai R, et al. *Nat Commun* 2016;7:11849. PMID: 27282753.
[1569] Konig MF, et al. Sci Transl Med 2016;8(369):369ra176. PMID: 27974664.

Figure 81. Pellet of lymphocyte cells created in the centrifuge. Credit: Rhoda Baer.

NIH has supported research examining specific cell types and their role in the development of autoimmune diseases. One study provided insight into B cells, also known as B lymphocytes—immune cells that must respond rapidly to infection without activating unnecessarily, which can lead to autoimmunity. NIAMS investigators uncovered three distinctly regulated steps, involving so-called epigenetic changes—heritable modifications that do not alter the DNA sequence itself—that control B-cell activation.[1570] Two of these steps rely on the transcription factor Myc, which before now had not been associated with epigenetic modifications in mammalian cells.

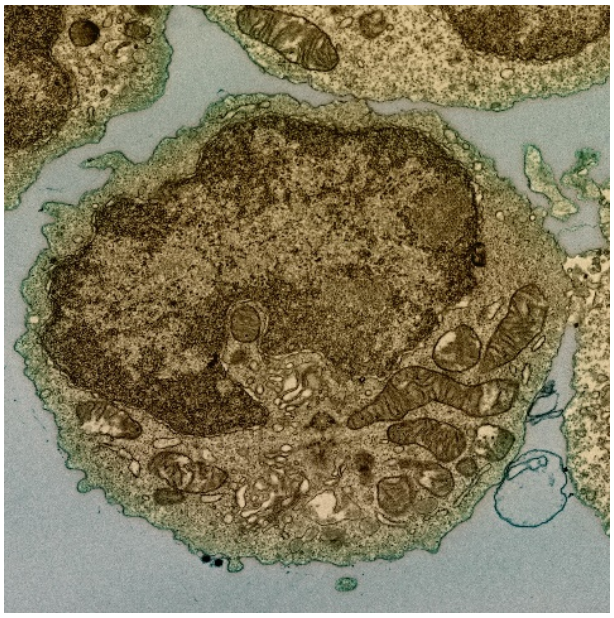

Figure 82. Transmission electron micrograph of a human B lymphocyte (also called a B cell). Credit: NIAID.

[1570] Kieffer-Kwon K, et al. *Mol Cell* 2018;67(4):566-78.e10. PMID: 28803781.

Several genetic studies have provided insight into the causes and increased risk for autoimmune diseases. NIEHS funding supported the first GWAS on the most common autoimmune muscle disease, called myostis, to study risk factors in people of European ancestry. The study confirmed that, in the population studied, the major histocompatibility complex—a set of genes coding for proteins on surface of cells—is the major genetic region associated with all the different clinical forms of myositis. Further analysis found that almost all the genetic risk for myositis is due to variations within the 8.1 ancestral haplotype—a specific set of genes that are inherited together on the same chromosome.[1571]

In another study, NIEHS-supported scientists have discovered that people who carry variants of two genes—the soluble form of the interleukin-7 (IL7R) receptor alpha chain gene (IL7R) and an RNA helicase (DDX39B)—may be almost three times more likely to have MS.[1572] These results highlight the molecular mechanisms that lead to a disease outcome.

Genetic studies have also led to the re-classification of autoimmune diseases. One form of juvenile idiopathic arthritis (JIA), a group of seven diseases characterized by swelling of the joints in children, may need to be reclassified based on the results of a research effort led by NIAMS.[1573] A GWAS identified several new single-nucleotide polymorphisms linked to Systemic JIA (sJIA), a rare, severe type of JIA. The results indicate that sJIA is genetically distinct from other JIA groups and suggest it should be reclassified as separate from other JIA disorders.[1574] The findings suggest that different approaches to finding treatment options for sJIA may be needed.

In addition to supporting research to better understand the mechanisms of known autoimmune diseases, NIH also supports the identification and understanding of previously unidentified autoimmune diseases. NIAMS intramural researchers recently described a new genetic disease characterized by both a compromised ability to fight infection and an overactive immune response against a body's own tissues. Patients with the disease—BACH2-related immunodeficiency and autoimmunity, or BRIDA—are susceptible to recurrent infections and bowel inflammation. While the investigators were studying the molecular basis of BRIDA, they discovered commonalities with other diseases that are associated with mutations in genes regulated by regions of DNA called super-enhancers.[1575] This discovery has implications for how investigators use whole-genome DNA sequencing data to identify disease-causing mutations.

There is growing consensus that autoimmune diseases likely result from interactions between genetic and environmental factors. To better understand this interaction, NIEHS supports research examining how genetic and environmental factors work together to compromise the body's ability to defend itself and develop into autoimmune diseases.[1576] For example, NIH-supported research is exploring the relationship

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[1571] Miller FW, et al. *Genes Immun* 2015;16(7):470-80. PMID: 26291516.
[1572] Galarza-Muñoz G, et al. *Cell* 2017:169(1):72-84.e13. PMID: 28340352.
[1573] https://www.niams.nih.gov/newsroom/spotlight-on-research/genetic-evidence-separates-systemic-juvenile-idiopathic-arthritis.
[1574] Ombrello M, et al. *Ann Rheum Dis* 2017;76(5): 906-13. PMID: 27927641.
[1575] Afzali B, et al. *Nat Immunol* 2017; 18(7):813-23. PMID: 28530713.
[1576] https://www.niehs.nih.gov/health/topics/conditions/autoimmune/index.cfm.

between environmental chemicals and antinuclear antibodies, which are the most common type of antibodies and frequently are seen in patients with systemic autoimmune disease. A recent study suggests that background levels of many chemical exposures typical in the U.S. population are not strongly associated with antinuclear antibodies.[1577]

In addition to environmental and genetic factors, the link between the genetic environment and the development of autoimmune diseases is being explored. Using a novel computational method, NIAID-supported researchers also showed that a viral protein found in Epstein-Barr virus (EBV)–infected human cells may activate genes associated with increased risk for autoimmunity.[1578] EBV, the cause of infectious mononucleosis, has been associated with subsequent development of lupus and other chronic autoimmune illnesses, but the mechanisms behind this association have been unclear.[1579] Understanding how EBV infection could contribute to the development of autoimmune diseases could lead to developing better therapies that disrupt that linkage.

Autoimmune Diseases and Pregnancy

Understanding how autoimmune diseases impact pregnancy outcomes can enable providers to personalize assessment, counseling, clinical care, and treatment for pregnant women with autoimmune diseases. When investigators launched PROMISSE (Predictors of Pregnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic Lupus Erythematosus), a multicenter prospective observational study, in 2003, no one knew what patient characteristics, disease signs, or symptoms were associated with poor pregnancy outcomes.[1580] The NIAMS-funded initiative has shown that the majority of women who have lupus can expect a good pregnancy outcome if their disease is inactive. Recently, investigators found that elevated levels of activation fragment Bb and sC5b-9 in plasma can predict adverse pregnancy outcomes in women who have lupus and/or antiphospholipid antibodies.[1581]

Similarly, researchers are conducting studies to determine how specific autoimmune diseases can affect pregnancy, further informing counseling and treatment. For example, researchers supported by NIAMS and NICHD conducted a study utilizing population-based Swedish registries to examine women experiencing their first pregnancy and comparing those who did not have lupus with those who were diagnosed with lupus before or within 5 years after giving birth. The researchers found that women with lupus or who would be diagnosed with lupus within 5 years were more likely to need cesarean sections and to experience preeclampsia, early birth, serious infections after giving birth, stroke, and thyroid

[1577] Dinse G, et al. *Environ Health Perspect* 2016;124(4):426. PMID 26252071.
[1578] Harley J, et al. *Nat Genet* 2018; 50(5):699-707.PMID: 29662164.
[1579] https://www.niaid.nih.gov/news-events/epstein-barr-virus-protein-can-%E2%80%9Cswitch-%E2%80%9D-risk-genes-autoimmune-diseases.
[1580] https://clinicaltrials.gov/ct2/show/NCT00198068.
[1581] Kim M, et al. *Ann Rheum Dis* 2018;77(4): 549-55.PMID 29371202.

problems.[1582] Additionally, their babies were more likely to have low birth weight and to have an infection within their first year compared with babies born to women without lupus.[1583]

Knowing how pregnancy complications could increase the risk of developing autoimmune diseases in the future could help refine clinical care. For example, NIAMS- and NICHD-supported researchers analyzed national Danish birth registry data and hospital records for 778,758 women who gave birth between 1978 and 2010. They reported that preeclampsia, a pregnancy complication related to high blood pressure, was associated with a 69-percent increase in the long-term risk of developing scleroderma.[1584]

Improving Screening, Diagnosis, and Treatment

NIH supports research on improving the screening, diagnosis, and treatments for autoimmune disorders. Improved screening and diagnosis for autoimmune disorders can lead to the administration of more appropriate and timely treatments while minimizing adverse outcomes. For example, in lupus, a heterogeneous disease with complex and variable clinical manifestations, the inability to group patients into clear-cut categories has been a major barrier to diagnosis and treatment and also has limited the success of clinical trials. Researchers seeking to address this issue recently identified differences in gene expression among pediatric patients with lupus.[1585] The differences correlate with changes in disease activity and can be used to stratify patients into distinct groups. The ability to classify patients in a clinically meaningful way based on molecular information is an important step toward the goal of developing precision medicine approaches to drug discovery and treatment for lupus.

Additionally, NIAMS intramural researchers conducted the first study analyzing the clinical features of scleroderma patients with muscle weakness and fibrosing myopathy. The study found that fibrosing myopathy scleroderma patients had more severe muscle weakness and higher mortality rates, and they did not express high levels of the muscle disease marker CK, which is commonly used by clinicians to define muscle disease severity.[1586] This study indicates that muscle biopsies may be necessary in fibrosing myopathy scleroderma patients to identify the cause of muscle weakness and determine the appropriate therapeutic interventions.

[1582] Arkema EV, et al. *Arthritis Care Res* 2016;68(7):988-94. PMID 27338103.
[1583] Arkema EV, et al. *Arthritis Care Res* 2016;68(7):988-94. PMID 27338103.
[1584] Kamper-Jørgensen M, et al. *Acta Obstet Gynecol Scand* 2018;97(5):587-90. PMID 29344946.
[1585] Banchereau R, et al. *Cell* 2016; 165(3):551-65.PMID: 27040498.
[1586] Paik J, et al. *Arthritis Care Res (Hoboken)* 2017;69(11):1764-70. PMID: 28544788.

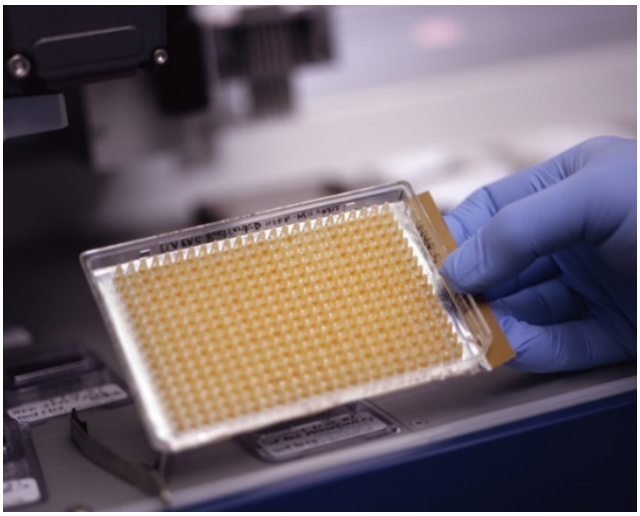

Figure 83. Assay plate loaded with single-nucleotide polymorphism samples. Credit: Rhoda Baer.

NIH-supported research has also led to the identification of biomarkers that may help clinicians develop better treatment strategies. For example, NIAMS intramural researchers identified a region with a single-nucleotide polymorphism (SNP)—a common type of genetic variation in which there is a single change of a nucleotide at a specific spot in DNA—affecting a gene called IL1RN as a true sJIA susceptibility region.[1587,1588] SNPs linked to high IL1RN expression were associated with non-response to anakinra therapy. The findings highlight IL1RN as a potential biomarker to help clinicians determine sJIA treatment strategies—particularly for children, who respond differently to sJIA therapies with some children not responding at all.[1589]

NIH continues to support research evaluating treatment options. Several drugs currently being used to treat specific autoimmune diseases are now being tested to determine whether they could also be used to effectively treat other types of autoimmune diseases. Recently, NIAMS investigators and colleagues from NHLBI and the NIH OD used a mouse model to examine if tofacitinib, which is approved for the treatment of RA, could alleviate symptoms associated with lupus.[1590] Based on positive findings in mice suggesting that tofacitinib could be a promising treatment for lupus, NIAMS clinicians have initiated a Phase Ib clinical trial to determine the safety and tolerability of tofacitinib for lupus patients with active disease.[1591]

In another NIAMS-supported study, researchers demonstrated that tofacitinib—as well as ruxolitinuib, which is used to treat different types of blood cancers—could induce rapid hair regrowth, offering a potential treatment option for alopecia areata, an autoimmune condition that causes hair loss and for

[1587] https://ghr.nlm.nih.gov/primer/genomicresearch/snp.
[1588] Arthur VL, et al. *Arthritis Rheumatol* 2018;70(8); 1319-30. PMID: 29609200.
[1589] Arthur VL, et al. *Arthritis Rheumatol* 2018;70(8); 1319-30. PMID: 29609200.
[1590] https://www.niams.nih.gov/newsroom/research-briefs/tofacitinib-shows-potential-treating-lupus.
[1591] Furumoto Y, et al. *Arthritis Rheumatol* 2017;69(1): 148-60. PMID: 27429362.

which there is no cure or approved drugs for its treatment.[1592,1593] Another example is dimethyl fumarate, or DMF, a treatment approved by the FDA for MS and by the European Commission for psoriasis. Because of DMF's effectiveness against MS and other diseases in which chronic inflammation is a key characteristic, researchers supported by NIAMS investigated whether DMF can modulate the skin fibrosis that is associated with scleroderma.[1594] Findings from the study support the potential use of DMF as a therapeutic treatment for systemic scleroderma dermal fibrosis, a devastating fibrotic disease with few treatment options.[1595,1596]

New treatment options are also being explored. NIAMS-funded researchers developed a potential new therapy for the autoimmune skin disease pemphigus vulgaris, which occurs when pathologic antibodies attack molecules that hold skin cells together. Harnessing the ability of cytotoxic T cells to kill other cells, researchers genetically engineered receptor T cells to enable them to selectively recognize and destroy the B lymphocytes that produce pemphigus-causing autoantibodies.[1597] They demonstrated that the modified T cells could specifically target the pathogenic B cells responsible for pemphigus, while sparing other, nonpathogenic B cells that protect against cancer and infections.[1598] If the results bear out in further testing, researchers hope that the therapy can be adapted to create safer and more effective treatments for pemphigus and other autoimmune diseases.

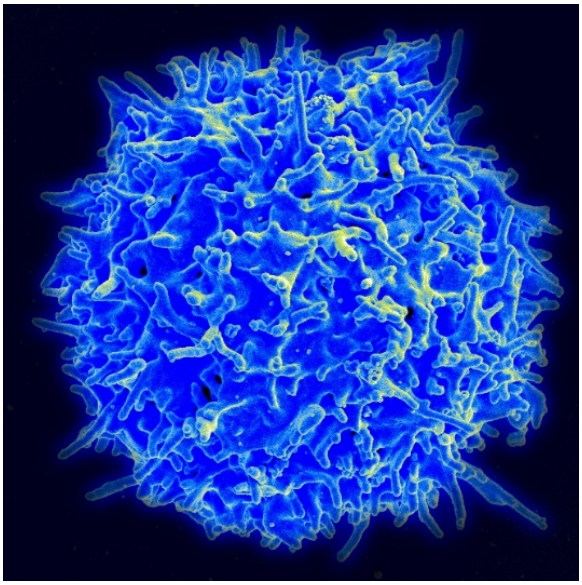

Figure 84. Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID.

[1592] Harel S, et al. *Sci Adv* 2015;1(9):e1500973. PMID: 26601320.
[1593] https://www.niams.nih.gov/newsroom/spotlight-on-research/two-drugs-that-treat-rheumatoid.
[1594] Toyama T, et al. *J Invest Dermatol* 2018;138(1):78-88. PMID: 28870693.
[1595] Toyama T, et al. *J Invest Dermatol* 2018;138(1):78-88. PMID: 28870693.
[1596] https://www.scleroderma.org/site/SPageNavigator/patients_whatis.html;jsessionid=00000000.app357a?NONCE_TOKEN=84FDBF12A5F29AFD97FB92CA38E58B4D#.XNSP6I5KhPY.
[1597] https://www.nih.gov/news-events/nih-research-matters/approach-targets-autoimmunity.
[1598] Ellebrecht C, et al. *Science* 2016;353(6295):179-84. PMID: 27365313.

Results from the NIAID-sponsored High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) clinical trial provide evidence that high-dose immunosuppressive therapy followed by transplantation of a person's own blood-forming stem cells can induce sustained remission of relapsing-remitting multiple sclerosis (RRMS).[1599] The experimental treatment aims to suppress active disease and prevent further disability by removing disease-causing cells and resetting the immune system. Five years after receiving the treatment, called high-dose immunosuppressive therapy and autologous hematopoietic cell transplant (HDIT/HCT), 69 percent of trial participants had survived without experiencing progression of disability, relapse of MS symptoms, or new brain lesions.[1600] Notably, participants did not take any MS medications after receiving HDIT/HCT. These findings indicate that HDIT/HCT could be a possible therapeutic option for RRMS, the most common form of MS.

As a final example, multiple organizations have joined to form consortia or partnerships to address the need for a better understanding of and treatments for autoimmune diseases. The Accelerating Medicines Partnership (AMP) is a public–private partnership that seeks to transform the current model for identifying and validating the most promising biological targets for the development of new drugs and diagnostics.[1601] Through AMP, NIAID and NIAMS are leading projects on the autoimmune conditions RA and lupus.[1602] To date, the network of clinicians, translational researchers, and bioinformaticians has developed novel tools and techniques that have transformed the way researchers are approaching autoimmune disease. With phase 1 of the initiative complete and phase 2 ongoing, data generated from cutting-edge technologies are being made publicly available for other researchers to interrogate.[1603] At the same time, the network has implemented research innovations that will have a lasting impact on the field, including collaboration plans involving dispersed research institutions, standardization of sample-processing protocols across multiple research sites, and patient recruitment strategies to enhance participation of underrepresented populations.

Infectious Diseases and Biodefense

Infectious diseases continue to pose a significant threat to human health, with many types of infections having far-reaching, global consequences. The emergence of new pathogens, the re-emergence of microbes, and the rise of antimicrobial resistance (AMR) are continual and ever-changing threats in our increasingly global society. Of the top 10 threats to global health identified by WHO in 2019, five were related to infectious diseases: influenza pandemic, antimicrobial resistance, dengue, HIV/AIDS, and Ebola and other high-threat pathogens.[1604] WHO reports that three of the top 10 causes of death worldwide are

[1599] https://www.niaid.nih.gov/news-events/stem-cell-transplants-may-induce-long-term-remission-multiple-sclerosis.
[1600] Nash R, et al. *Neurology* 2017;88(9):842-25. PMID: 28148635.
[1601] https://www.nih.gov/research-training/accelerating-medicines-partnership-amp.
[1602] https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/autoimmune-diseases-rheumatoid-arthritis-lupus.
[1603] https://www.niams.nih.gov/grants-funding/funded-research/accelerating-medicines.
[1604] https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019.

currently infectious diseases: lower respiratory infections, neonatal conditions, and diarrheal diseases.[1605] In lower-income countries, six infectious diseases—neonatal conditions, lower respiratory conditions, diarrhoeal diseases, malaria, tuberculosis (TB), and HIV/AIDS—are among top 10 causes of death.[1606] In addition to naturally or accidently occurring infectious diseases, the deliberate release of pathogenic agents, such as anthrax or smallpox, could cause large-scale public health emergencies. NIH-supported research in infectious diseases and biodefense is essential to developing new prevention strategies, treatments, and diagnostics to combat these growing threats.

Summary of NIH Activities

NIH continues its long history of combating infectious diseases by helping develop new and improved prevention and treatment strategies, as well as diagnostics and other technologies. NIH's wide-ranging infectious disease portfolio includes research in HIV/AIDS; malaria; TB; viral hepatitis; and emerging and re-emerging infectious diseases and related concerns, such as influenza, Ebola, Zika, and AMR. NIH-supported research on infectious and emerging diseases and biodefense covers a wide array of areas, from learning how a pathogen causes disease to developing innovative approaches to prevent diseases to creating new possibilities for the treatment of disease.

Research on infectious diseases and biodefense is primarily conducted and supported by NIAID. However, other NIH entities—including FIC, NCATS, NCCIH, NCI, NEI, NHLBI, NIA, NIAMS, NIBIB, NICHD, NIDA, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NIMHD, NINDS, NINR, and NLM—also support research in this area, as do OAR and OBSSR within the NIH OD. NIH funding for infectious diseases research was $5,518 million in FY 2016, $5,684 million in FY 2017, and $6,024 million in FY 2018.[1607] NIH funding for biodefense research was $1,951 million in FY 2016, $1,964 million in FY 2017, and $2,170 million in FY 2018.[1608]

Vector-Borne Disease Research

The *21st Century Cures Act* (P.L. 114-255, Sec. 2062 (a) and (b)) mandates that NIH conduct or support epidemiological, basic, translational, and clinical research related to vector-borne diseases, including tickborne diseases, and provide information on NIH actions with respect to tickborne diseases. In response to this mandate, Appendix C includes the following information on NIH actions in FY 2016, 2017, and 2018 regarding tickborne diseases and other vector-borne diseases:

- Epidemiological, basic, translational, and clinical research updates
- Committees convened

[1605] https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.
[1606] https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.
[1607] https://report.nih.gov/categorical_spending.aspx.
[1608] Reporting for this category does not follow the standard RCDC process. The total amount reported is consistent with reporting requirements for this category to the U.S. Office of Management and Budget. The project listing includes non-project or other support costs associated with the annual total for this category. Additional information on this category is available at https://www.niaid.nih.gov/research/biodefense.

- Programs active
- Workshops held

Major Infectious Diseases

Major infectious diseases—such HIV/AIDS, malaria, TB, and viral hepatitis—significantly impact the health and well-being of millions of people around the world. In 2017, deaths related to HIV, malaria, TB and viral hepatitis exceeded 2.8 million worldwide.[1609]

HIV/AIDS

Despite progress toward prevention and treatment strategies, HIV/AIDS remains a significant public health issue, both globally and in the U.S., where an estimated 1.1 million people were living with HIV in 2015, according to the CDC.[1610] Combating the HIV/AIDS epidemic remains an NIH priority, and NIH has developed a robust HIV portfolio. Supported research includes increasing prevention through pre-exposure prophylaxis (PrEP), developing a vaccine, creating new and improving current diagnostic and treatment options, and reducing transmission of HIV in all populations. NIH funding for HIV/AIDS research was $3,000 million in FYs 2016 and 2017 and $2,995 million in FY 2018.[1611]

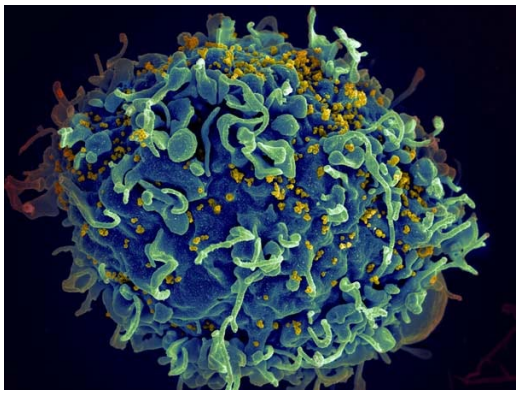

Figure 85. A human T cell (blue) is under attack by HIV (yellow), the virus that causes AIDS. The virus specifically targets T cells, which play a critical role in the body's immune response against invaders, like bacteria and viruses. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, NIAID.

The annual *Trans-NIH Strategic Plan for HIV and HIV-Related Research* guides the NIH investment in the field, building on scientific progress and opportunities for advancing HIV/AIDS research toward an end to

[1609] http://ghdx.healthdata.org/gbd-results-tool.
[1610] https://www.cdc.gov/hiv/statistics/overview/ataglance.html.
[1611] The total for HIV/AIDS research includes both extramural and intramural research (including research management and support, Management Fund, and Service and Supply Fund), buildings and facilities, research training, and program evaluation, as well as research on the many HIV-associated co-infections and comorbidities, including TB, hepatitis C, and HIV-associated cancers. It also includes all the basic science underlying this research. Other RCDC categories are not reported this way. As a result, the total for HIV/AIDS-related research is not comparable to spending reported for other RCDC diseases. More information on this area is available at https://www.oar.nih.gov.

the pandemic. It informs the scientific community, the public, Congress, people with HIV/AIDS, and organizations working in the HIV field about NIH's HIV/AIDS research agenda. OAR, congressionally mandated to manage HIV/AIDS resources for intramural and extramural research across NIH, collaborates with ICOs to develop the strategic plan. The 2016 and 2017 strategic plans provided a roadmap for the NIH HIV/AIDS research program, ensuring that funds were allocated in accordance with established NIH scientific research priorities.[1612,1613] In May 2018, OAR released a request for information (RFI) to solicit input from the NIH scientific community, other government agencies, nongovernment experts, the community, and other stakeholders on the NIH HIV/AIDS research priorities, important scientific developments, gaps, and emerging areas of HIV research.[1614] The recommendations generated from the RFI responses offered a good assessment of current research being conducted and supported by NIH, provided a path forward for future research, and highlighted new areas to consider for increased funding. The collective input is being used for the development of the *FY 2021–2025 NIH Strategic Plan for HIV and HIV-Related Research*.

OAR also prepares an annual Professional Judgment Budget. Based solely on current research opportunities and the NIH HIV/AIDS research priorities, the document estimates the funds needed to fully pursue the scientific opportunities that could lead to the end of the HIV pandemic. The *2018 NIH HIV/AIDS Professional Judgement Budget* addressed critical scientific gaps across the priority areas, capitalized on emerging research opportunities by providing additional funding for newly identified areas of study, and enhanced the research foundation needed to implement the major goals of the *National HIV/AIDS Strategy for the United States: Updated to 2020* and the accompanying *Federal Action Plan*.[1615]

In addition to supporting HIV/AIDS research, NIH is an active participant of World AIDS Day, an internationally recognized day aimed at increasing awareness of the AIDS pandemic. In 2017, NIAID and OAR released a joint NIH statement marking the 30th celebration of World AIDS Day. The statement highlighted the accomplishments of researchers over the past three decades that have changed the course of HIV in patients and now allow a person with HIV to achieve a nearly normal lifespan.[1616] The statement also provided an overview of the successes and challenges needed to change the course of the HIV epidemic, potentially leading to the end of the HIV pandemic worldwide. In 2018, people from across NIH and the community gathered at the NIH campus in Bethesda for the OAR-sponsored World AIDS Day symposium *More Than Three Decades: Inspiring HIV Discoveries Through Basic Science Research*. Speakers representing various scientific disciplines discussed the role of basic science research in yielding effective treatment and prevention tools, and potentially a cure, in the ongoing fight against HIV.[1617]

[1612] https://www.oar.nih.gov/sites/default/files/FY2016-Trans-NIH-Plan-for-HIV-Related-Research_508.pdf.
[1613] https://www.oar.nih.gov/sites/default/files/FY2017_OARStrategicPlan_508.pdf.
[1614] https://www.federalregister.gov/documents/2018/05/21/2018-10784/request-for-information-for-the-development-of-the-fiscal-year-2021-2023-trans-nih-strategic-plan.
[1615] https://www.oar.nih.gov/sites/default/files/OAR%20Pro%20Judgment%20Budget_V2_508.pdf.
[1616] https://www.niaid.nih.gov/news-events/nih-statement-world-aids-day.
[1617] https://www.oar.nih.gov/news-and-events/world-aids-day-2018.

Figure 86. A watercolor painting speaking to global AIDS awareness. Credit: NIAID.

Preventing HIV Infection

Preventing new HIV infections is a critical step toward ending the HIV pandemic. Today, an array of prevention methods is available for use in combination or on their own, and scientists continue to work to develop and improve cutting-edge tools and techniques to prevent HIV in diverse populations around the world.[1618]

The Martin Delaney Collaboratories for HIV Cure Research program was originally launched in 2011 with the funding of three complementary research groups at the Fred Hutchinson Cancer Research Center; The University of North Carolina at Chapel Hill; and the University of California, San Francisco. The research program—supported by NIAID, NIDA, NIMH, and NINDS—encourages collaborative efforts to address the multifaceted puzzle of curing HIV.[1619] In 2016, the program was expanded as part of President Obama's pledge of $100 million for HIV cure research to include three additional research groups at The George Washington University, The Wistar Institute, and the Beth Israel Deaconess Medical Center.[1620] Total funding of the program was doubled to $30 million per year. The new collaborative projects will launch novel investigations into HIV cure strategies that include immunotherapy, therapeutic vaccines, and gene modification.[1621]

NIH continues to support efforts to better comprehend the immune response to HIV and how it might inform prevention strategies. New research in monkeys exposed to simian immunodeficiency virus (SIV), the monkey equivalent of HIV, suggests that the virus spreads rapidly in the body and triggers early host responses that suppress antiviral immunity, thus promoting viral replication.[1622] The NIAID-funded study

[1618] https://www.niaid.nih.gov/diseases-conditions/hiv-prevention.
[1619] https://www.nih.gov/news-events/news-releases/nih-expands-investment-hiv-cure-research.
[1620] https://www.nih.gov/news-events/news-releases/nih-expands-investment-hiv-cure-research.
[1621] https://www.nih.gov/news-events/news-releases/nih-expands-investment-hiv-cure-research.
[1622] https://www.niaid.nih.gov/news-events/animal-study-paints-picture-earliest-immune-responses-hiv.

provides a detailed view of the period between initial mucosal exposure to the virus and the point at which it becomes detectable in the blood. The scientists found that SIV disseminates rapidly through the body, and they observed an inflammatory immune response in virus-infected tissues as early as one day after exposure to SIV.[1623] These findings suggest that the window of opportunity to contain or eliminate the virus at its mucosal port of entry is more limited than previously appreciated. Increased understanding of these early events—which are difficult, if not impossible, to study in people with HIV—will impact the continued development of strategies to prevent HIV infection.[1624]

PrEP is a highly effective prevention strategy whereby people who are not infected with HIV take medications to prevent the acquisition of HIV. However, the challenge of taking HIV medicines daily limits the efficacy of this approach, so NIAID is investigating longer-acting, easier-to-use HIV therapies and injectable medication for HIV prevention. Two ongoing, large-scale clinical trials—one of which is the first large-scale clinical trial of a long-acting injectable medication for HIV prevention in sexually active women—are comparing daily oral PrEP to injections of the investigational anti-HIV drug cabotegravir once every eight weeks.[1625,1626] The two studies launched in 2016 and 2017 and were initiated by the HIV Prevention Trials Network (HPTN), which is supported by NIH. The studies could lead to a new HIV prevention tool for both men and women.

In 2016, two multinational studies were launched as part of the Antibody-Mediated Prevention clinical trial that hopefully will provide insight into long-acting HIV prevention methods and vaccine research. The two studies are testing whether an investigational anti-HIV antibody called VRC01, which is given intravenously every eight weeks, is safe and effective in preventing HIV.[1627] The studies, sponsored and funded by NIAID, are being conducted collaboratively by the NIAID-funded HIV Vaccine Trials Network and the NIDA- and NIMH-funded HPTN. One study will be carried out at 24 sites in Brazil, Peru, and the U.S. and will enroll 2,700 men and transgender people who have sex with men.[1628] The second study is enrolling 1,500 sexually active women at sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe.[1629]

Prevention methods at the population level are also key to substantially reducing new HIV infections, as recently shown by several long-term studies. In the Rakai district of Uganda, NIAID-supported researchers found that combining voluntary medical male circumcision with ART decreased HIV incidence by 42 percent.[1630] In parallel, NIAID is co-funding the Population Effects of Antiretroviral Therapy to Reduce HIV Transmission study, which is examining a broad array of HIV prevention measures, including voluntary male circumcision, prevention of mother-to-child transmission, and linkage to care in South African and

[1623] Barouch DH, et al. *Cell* 2016;165(3): 656-67. PMID: 27085913.
[1624] https://www.niaid.nih.gov/news-events/animal-study-paints-picture-earliest-immune-responses-hiv.
[1625] https://www.hptn.org/research/studies/hptn084.
[1626] https://www.hptn.org/research/studies/hptn083.
[1627] https://www.niaid.nih.gov/news-events/nih-launches-large-clinical-trials-antibody-based-hiv-prevention.
[1628] https://www.niaid.nih.gov/news-events/nih-launches-large-clinical-trials-antibody-based-hiv-prevention.
[1629] https://www.niaid.nih.gov/news-events/nih-launches-large-clinical-trials-antibody-based-hiv-prevention.
[1630] Grabowski MK, et al. *N Engl J Med* 2017; 977(22): 2154-66. PMID: 29171817.

Zambian communities.[1631] Early findings are encouraging: After one year, nearly 90 percent of women and 80 percent of men with HIV know their HIV status, and about 75 percent of these individuals are on ART.

Research into prevention and treatment strategies for all population types and age groups is vital to combating the HIV epidemic. The Seek and Treat for Optimal Prevention for HIV/AIDS, or STOP HIV/AIDS, project demonstrated that seeking and treating drug users with HIV led to a significant decline in the incidence of HIV in British Columbia.[1632] The NIDA-sponsored program, which was renewed in 2012 and continued through 2017, provided key evidence on the effectiveness of efforts to seek, test, treat, and retain individuals at risk for HIV infection, including injection drug users (IDUs) and men who have sex with men. Researchers confirmed that treatment of HIV not only improves outcomes of those with HIV but also is an effective prevention strategy for HIV transmission and that individuals, including IDUs, can be effectively treated with antiretrovirals. This study demonstrated that seek, test, treat, and retain initiatives can have a positive impact on the health and longevity of people with HIV, including IDUs.

CDC reported that in 2017, 21 percent of new HIV diagnoses in the U.S. occurred among those ages 13–24 years old and this cohort was among the least likely to access care in a timely manner.[1633] Investigators, funded in part or in whole by NIAID, reported in 2017 that a monthly vaginal ring and a daily oral tablet, both containing anti-HIV drugs, were safe and acceptable in studies of adolescents.[1634] The experimental ring is designed for HIV prevention, and the oral tablet is already used for this purpose in adults. These studies mark the first time the vaginal ring was tested in adolescent girls younger than 18 years and the first time a clinical trial of the oral tablet as PrEP specifically for adolescents included girls.[1635] The findings pave the way for larger trials of the vaginal ring and oral PrEP in this vulnerable age group.

The NIH also funds the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), which is the only national, multicenter research network devoted to the health and well-being of adolescents and young adults with HIV and those at risk. The primary mission of the ATN is to conduct both independent and collaborative research that explores promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in adolescents and young adults ages 12–24 years with HIV or at risk.[1636] ATN research informed FDA approval of Truvada®, a drug combination used in PrEP for HIV, for use in at-risk adolescents in 2018.[1637]

[1631] https://www.nih.gov/news-events/news-releases/study-evaluates-population-wide-testing-early-treatment-hiv-prevention.
[1632] https://projectreporter.nih.gov/project_info_outcomes.cfm?aid=9228352&icde=46663033.
[1633] https://www.cdc.gov/hiv/group/age/youth/index.html.
[1634] https://www.niaid.nih.gov/news-events/adolescents-oral-truvada-and-vaginal-ring-hiv-prevention-are-safe-acceptable.
[1635] https://www.niaid.nih.gov/news-events/adolescents-oral-truvada-and-vaginal-ring-hiv-prevention-are-safe-acceptable.
[1636] https://www.nichd.nih.gov/research/supported/atn.
[1637] https://www.nichd.nih.gov/newsroom/news/051618-PrEP.

Injectable contraceptives have become one of the most widely used methods of contraception in sub-Saharan Africa due to their ease of use, effectiveness, and ability to be used discreetly.[1638] However, observation data indicated that women who use a common type of injectable contraception—depot medroxyprogesterone acetate (DMPA)—could be at increased risk of acquiring HIV.[1639] In 2018, NIH-supported researchers published results from a study investigating whether any differences exist between the formulations of DMPA and the risk of HIV acquisition. The researchers believe, based on available data, that the intramuscular and subcutaneous formulations of DMPA are not likely to differ. [1640] Understanding the risks that women who use this type of contraceptive face will be important for developing prevention strategies.

Finally, people living with HIV/AIDS continue to face stigma and discrimination, which can significantly impact their well-being. Utilizing text mining and data visualization methodologies, NLM researchers conducted an analysis of more than 80,000 abstracts presented at the International AIDS Conference from 1989 to 2014 to evaluate how HIV-related terminology has changed over time.[1641] The research found that the changes in HIV/AIDS terminology echo the progress made in research. Although the findings reflect the impact of efforts to decrease the stigmatization associated with the disease, they also highlighted the need for continued efforts to destigmatize HIV/AIDs. In support of those efforts, FIC, NCI, NICHD, NIMH, and OBSSR announced a new FOA in 2018 to support new and impactful research to better understand how to reduce stigma as a factor in HIV transmission, to eliminate or mitigate the aspects of stigma that limit beneficial health outcomes, and to initiate exploratory studies to determine the feasibility of stigma interventions. [1642] The FOA will hopefully stimulate research, which will lead to better outcomes for the prevention and treatment of HIV/AIDS and improve the quality of life of people with HIV/AIDS in LMICs.[1643]

[1638] Polis C, et al. *Contraception* 2018: 97(3):191-97. PMID: 29242082.
[1639] Polis C, et al. *Contraception* 2018: 97(3):191-97. PMID: 29242082.
[1640] Polis C, et al. *Contraception* 2018: 97(3):191-97. PMID: 29242082.
[1641] Dancy-Scott N, et al. *JMIR Public Health and Surveillance* 2018;4(2):e50. PMID: 29728344.
[1642] https://grants.nih.gov/grants/guide/pa-files/PAR-18-732.html.
[1643] https://grants.nih.gov/grants/guide/pa-files/PAR-18-732.html.

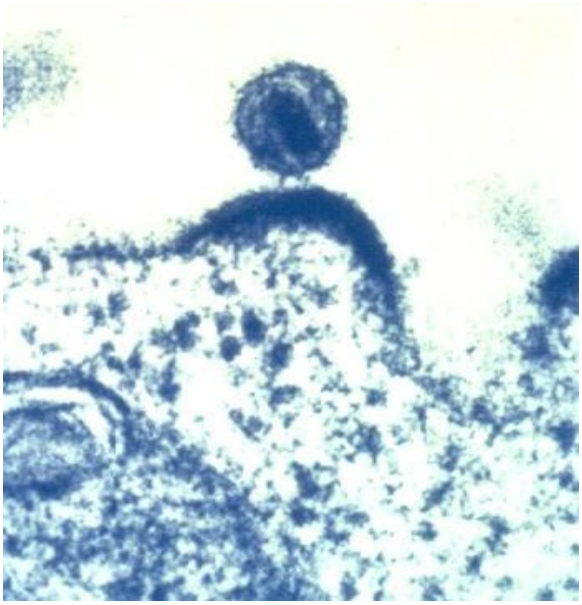

Figure 87. HIV is shown budding out of a human immune cell, which the virus infects and uses to replicate. Credit: NIAID.

HIV Vaccine

Historically, vaccination has been the best method for protecting people from infectious diseases. Although an array of techniques are available for preventing HIV infection, the development of a safe and effective HIV vaccine remains key to realizing a durable end to the HIV pandemic.[1644] To mark the 2018 HIV Vaccine Awareness Day, NIAID and OAR released a joint NIH statement providing an update on the development of effective, efficacious vaccines, the status of two large HIV vaccine clinical trials, and strategies using the passive transfer of broadly neutralizing antibodies (bNAbs) that could potentially protect against HIV.[1645] They also noted that advances and ongoing investigations provided cautious optimism that the development of an HIV vaccine is making headway.

In pursuit of such a key component to ending the HIV pandemic, NIH continues to support HIV vaccine research activities. The *FY 2016 Congressional Justification Budget* request outlined a number of research activities NIH would support in this area, including, but not limited to, new initiatives to integrate systems biology with HIV vaccine discovery and research to develop new tests to measure immune responses to the HIV vaccine candidates more accurately.[1646] To build on the knowledge gained from previous studies, NIH allocated resources toward the development and testing of improved vaccine candidates in additional clinical studies in the U.S. and abroad. The resources provided to vaccine research support critical research opportunities aimed at the development of safe, effective, and affordable vaccines that may be used in combination with other HIV/AIDS prevention strategies.

[1644] https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-development.
[1645] https://www.niaid.nih.gov/news-events/nih-statement-hiv-vaccine-awareness-day-may-18-2018.
[1646] https://www.oar.nih.gov/sites/default/files/2016_OAR_Volume_I_final_508.pdf.

NIH has undertaken and supported several research activities, the results of which will help inform future vaccine development. For example, researchers at Duke University, supported by OAR and NIAID as part of the Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery portfolio, have shown that antibody interactions with cells mediated by the antibody constant (Fc) region could harness multiple aspects of the immune system to provide protection through mechanisms other than neutralization.[1647] The team evaluated the responses between humans and nonhuman primates and published their key findings in 2017.

Research aimed at better knowing how bNAbs develop and evolve promises to aid HIV vaccine development efforts. bNAbs undergo a complex development and maturation process before achieving their mature, HIV-fighting form, and a minority of people with HIV naturally produce bNAbs that target multiple, diverse HIV strains. In 2016, NIAID-supported researchers reported that people with HIV infection who produce bNAbs have different immunological profiles than those who do not produce bNAbs.[1648] The researchers were able to identify specific immune cell subsets and functions that correlated with high levels of bNAbs.[1649] Defining how to safely replicate these attributes in HIV-uninfected vaccine recipients may lead to improved experimental vaccines to protect against HIV. In a separate study, NIH scientists and NIH-supported researchers and colleagues analyzed blood samples collected over time from a single individual with HIV. They monitored the evolution of a particular bNAb from acute to chronic HIV infection. Furthermore, they found that development of this bNAb had affected development of a separate type of bNAb, which neutralizes HIV in a different manner.[1650] The analysis revealed critical features in the bNAb development process that could be exploited by vaccination strategies to elicit the immune systems of uninfected people to produce bNAbs against HIV.

NIH also continues to support the development of experimental HIV vaccine candidates. NIAID reported in 2018 that an experimental vaccine regimen based on a vulnerable site on HIV's surface, called the fusion peptide, elicited antibodies in mice, guinea pigs, and monkeys that neutralize dozens of HIV strains.[1651] The fusion peptide—a short string of amino acids—is part of the spike on the surface of HIV that the virus uses to enter human cells. According to the scientists, the fusion peptide epitope is particularly promising for use as a vaccine because its structure is the same across most strains of HIV and because the immune system clearly recognizes it and makes a strong immune response to it.[1652] Building on this work, NIAID reported that a fusion peptide–based vaccine regimen elicited antibodies in monkeys that neutralized up to 59 percent of viruses from a globally representative panel of 208 HIV strains.[1653] The results demonstrate that a fusion peptide–based vaccine strategy might be a viable vaccine option in the future.

The first HIV vaccine efficacy study to launch anywhere in seven years is now testing whether an experimental vaccine regimen safely prevents HIV infection among South African adults. Begun in 2016,

[1647] Shen X, et al. *J Virol* 2017; 1(19):e00401-17. PMID: 28490585.
[1648] Moody MA, et al. *Sci Immunol* 2016;1(1):aag0851. PMID: 28783677.
[1649] Moody MA, et al. *Sci Immunol* 2016;1(1):aag0851. PMID: 28783677.
[1650] Bonsignori M, et al. *Cell* 2016;165(2):449-63. PMID: 26949186.
[1651] https://www.niaid.nih.gov/news-events/hiv-vaccine-elicits-antibodies-animals-neutralize-dozens-hiv-strains.
[1652] https://www.niaid.nih.gov/news-events/hiv-vaccine-elicits-antibodies-animals-neutralize-dozens-hiv-strains.
[1653] https://www.niaid.nih.gov/news-events/hiv-r4p-2018-kicks.

the study involves a new version of the only HIV vaccine candidate ever shown to provide some protection (31 percent protective) against the virus.[1654] The study, which NIH is co-funding, aims to enroll 5,400 men and women, making it the largest and most advanced HIV vaccine clinical trial to take place in South Africa, where more than 1,000 people become infected with HIV every day.[1655]

NIH and partners launched another large clinical trial in 2017 to assess whether an experimental HIV vaccine regimen is safe and able to prevent HIV infection. The new Phase IIb proof-of-concept study, called Imbokodo, aims to enroll 2,600 HIV-negative women in sub-Saharan Africa.[1656] Of 1.8 million new HIV infections worldwide in 2016, 43 percent occurred in eastern and southern Africa, with women and girls disproportionately affected.[1657] The vaccine regimen being tested in Imbokodo is based on mosaic immunogens—vaccine components designed to induce immune responses against a wide variety of global HIV strains.[1658] Work from the experimental vaccine regimens will help inform development and hopefully lead to a safe and effective vaccine against HIV.

Improving HIV Diagnosis and Treatment

Although the development of antiretroviral drugs has turned HIV into a chronic disease for many people with HIV, the search for new and more effective therapeutics remains a priority due to the development of resistance and unwanted side effects in current drugs.[1659] NIH continues to support research efforts, including developing new HIV diagnostics and treatment options, exploring approaches to suppress HIV, and understanding how HIV impacts other areas of the body.

Salivary diagnostics combine the power of chemistry, biology, computational science, and engineering within a portable device that can analyze, at the point of care, indicators of a variety of diseases and conditions affecting the mouth and the whole body.[1660] Salivary diagnostics are particularly appealing given their ability to produce results rapidly, the ease of specimen collection, and their cost-effectiveness. NIDCR is leveraging investments in salivary diagnostics to develop a simplified system that detects anti-HIV antibodies and viral genetic information in a single specimen of blood or saliva. Researchers supported by NIDCR have constructed a microfluidics system to detect both anti-HIV antibodies and HIV RNA in the same specimen of either blood or saliva.[1661] This new tool can identify HIV infections early by detecting HIV RNA present in the beginning stages of infection, before anti-HIV antibodies have developed, and could lead to a significant reduction in the transmission of HIV.[1662]

[1654] https://www.niaid.nih.gov/news-events/first-new-hiv-vaccine-efficacy-study-seven-years-has-begun.
[1655] https://www.niaid.nih.gov/news-events/first-new-hiv-vaccine-efficacy-study-seven-years-has-begun.
[1656] https://clinicaltrials.gov/ct2/show/record/NCT03060629?term=HVTN+705&rank=1.
[1657] https://www.niaid.nih.gov/news-events/nih-and-partners-launch-hiv-vaccine-efficacy-study.
[1658] https://www.niaid.nih.gov/news-events/nih-and-partners-launch-hiv-vaccine-efficacy-study.
[1659] https://www.niaid.nih.gov/diseases-conditions/hiv-treatment.
[1660] https://www.nidcr.nih.gov/grants-funding/funded-research/research-investments-advances/salivary-diagnostics.
[1661] Zongyuan C, et al. *J AIDS Clin Res* 2016;7(1):540. PMID: 26925300.
[1662] Zongyuan C, et al. *J AIDS Clin Res* 2016;7(1):540. PMID: 26925300.

NIH continues to support researchers as they search for new and more effective treatment options. In 2018, new findings from a NIAID-supported Phase I pilot clinical trial, led by scientists at The Rockefeller University, reported that a small group of people with HIV tolerated multiple infusions of two anti-HIV bNAbs.[1663] Infusions of the two potent anti-HIV bNAbs suppressed HIV for more than 15 weeks after stopping ART.[1664] In September 2018, scientists at NIAID launched a separate study evaluating a combination of these two bNAbs in people with HIV. The study will evaluate whether periodic infusions of the bNAbs are safe and gather preliminary data on how effectively the bNAb infusions, delivered together every two to four weeks, suppress HIV following discontinuation of ART.[1665] Further research is needed; however, these study findings could open new treatment possibilities for those with HIV.

Furthermore, studies have identified novel targets or signaling pathways involved in HIV infection or latency that could be potentially exploited to develop novel therapeutics. Notably, recent work by a NIDA-funded grantee has led to a nano-formulation that eradicates HIV in a mouse model of human HIV infection.[1666] The nano-formulation, as described in their 2018 publication, is a "long-acting, slow, effective release ART," which could have potential impacts on antiretroviral drug adherence.[1667]

To expand the HIV treatment portfolio, NIH is also exploring different HIV treatment options. When a SIV-infected monkey or a person with HIV receives ART, the therapy can suppress the virus to undetectable levels.[1668] Yet the virus still lurks silently in the genetic material of infected immune cells—known as viral reservoirs—even when suppressed. If ART is discontinued, SIV or HIV rapidly rebounds to high levels within a few weeks.[1669] Scientists at NIH and Emory University have experimentally induced sustained remission of SIV in infected monkeys. The animals' immune systems have been suppressing the virus to undetectable levels for as long as 23 months since the monkeys completed an investigational treatment regimen.[1670] In addition, the regimen has led to the near-complete replenishment of key immune cells that SIV had destroyed—something unachievable with ART alone.[1671] The study's results could not only inform alternative HIV treatment options, eliminating the need for daily ART treatments, but also inform HIV vaccine development.[1672] Other research has sought to find ways to boost the effectiveness of T cells—a type of cell that helps the immune system fight off infections and is attacked by HIV—against HIV, which could be extremely helpful in treating, controlling, and curing HIV infection. In 2017, NIAID-supported researchers reported that they had re-engineered CARs—receptors that have been engineered so T cells can better recognize infected T cells—targeting HIV-infected cells to be more potent at

[1663] https://www.niaid.nih.gov/news-events/combination-hiv-antibody-infusions-safely-maintain-viral-suppression-select-individuals.
[1664] Mendoza P, et al. *Nature* 2018;561(7724):479-84. PMID: 30258136.
[1665] https://www.niaid.nih.gov/news-events/nih-launches-study-test-combination-antibody-treatment-hiv-infection.
[1666] Lin Z, et al. *Chem Commun (Camb)* 2018; 54(60):8371-4. PMID: 29995046.
[1667] Lin Z, et al. *Chem Commun (Camb)* 2018; 54(60):8371-4. PMID: 29995046.
[1668] https://www.niaid.nih.gov/news-events/scientists-nih-and-emory-achieve-sustained-siv-remission-monkeys.
[1669] Byrareddy SN, et al. *Science* 2016;354(6309):197-202. PMID: 27738167.
[1670] Byrareddy SN, et al. *Science* 2016;354(6309):197-202. PMID: 27738167.
[1671] Byrareddy SN, et al. *Science* 2016;354(6309):197-202. PMID: 27738167.
[1672] https://www.niaid.nih.gov/news-events/scientists-nih-and-emory-achieve-sustained-siv-remission-monkeys.

controlling HIV replication.[1673] A clinical trial is planned to evaluate the ability of these HIV-specific CAR-T cells to provide durable control of HIV replication.

In the last three decades, survival for those with HIV infections has greatly improved, but a cure has remained elusive, in part because of the virus' ability to go dormant following infection, often residing in oral tissues. In 2016, NIDCR-funded scientists demonstrated that the mTOR protein complex regulates HIV reactivation from dormancy and that treatment with mTOR inhibitors prevented HIV reactivation in cultured patient cells.[1674] This finding could pave the way for new therapeutic approaches to keep HIV permanently dormant.

Previous research has clearly demonstrated that using ART to suppress HIV prevents perinatal HIV transmission and benefits the health of both mother and child.[1675] NIH launched a large international study in 2018 to compare the safety and efficacy of three ART regimens for pregnant women with HIV and the safety of these regimens for their infants. The study will evaluate the current preferred first-line regimen for pregnant women recommended by WHO and two regimens containing newer antiretroviral drugs that are becoming more widely used. It will provide data on the use of these newer drugs during pregnancy, helping to ensure that women with HIV and their infants receive the best available treatments.[1676]

Scientists reported in 2017 that a 9-year-old South African child who was diagnosed with HIV infection at one month of age and received anti-HIV treatment during infancy has suppressed the virus without anti-HIV drugs for eight-and-a-half years.[1677] The clinical trial in which the child received treatment and follow-up monitoring was funded by NIAID. The case appears to be the third reported instance of sustained HIV remission in a child after early, limited anti-HIV treatment.[1678] The case is another step toward determining how long-term HIV remission can be induced in children born with HIV.

Current HIV treatment guidelines call for all asymptomatic individuals with HIV to begin ART at the time of diagnosis instead of waiting for their disease to progress before getting treatment.[1679] However, new research, published in 2017 and supported by NIAMS, shows that people who begin ART upon receiving their HIV diagnosis lose bone in the spine and hip more quickly than those who waited to begin ART until after their immune system has deteriorated.[1680] Assuming the decreased bone mineral density in this population is associated with increased fragility, the need for strategies to preserve the bones of people infected with HIV is expected to gain attention as more people live longer due to the unequivocal benefits of early ART.

[1673] Leibman R, et al. *PloS Pathog* 2017;13(10):e1006613. PMID: 29023549.
[1674] Besnard E, et al. *Cell Host Microbe* 2016;20(6):785-97. PMID: 27978436.
[1675] https://www.niaid.nih.gov/diseases-conditions/prevention-perinatal-transmission.
[1676] https://www.niaid.nih.gov/news-events/nih-begins-large-hiv-treatment-study-pregnant-women.
[1677] https://www.niaid.nih.gov/news-events/child-living-hiv-maintains-remission-without-drugs-2008.
[1678] https://www.niaid.nih.gov/news-events/child-living-hiv-maintains-remission-without-drugs-2008.
[1679] Hoy JF, et al. *J Bone Miner Res* 2017;32(9):1945-55. PMID: 28650589.
[1680] Hoy JF, et al. *J Bone Miner Res* 2017;32(9):1945-55. PMID: 28650589.

It is estimated that in 2016, more than 50 percent of the more than 35 million people in the world with HIV will be older than 50 years of age.[1681] However, even those who achieve excellent long-term virologic control and immune recovery will experience higher rates of comorbidities at an earlier age than their counterparts without HIV, and 50–60 percent of deaths among persons with HIV will occur from these non-AIDS causes.[1682] In 2017, NINR released the Symptom Management in HIV-Infected Individuals with Comorbid Conditions FOA, seeking research applications focused on developing, adapting, and testing innovative, cost-effective strategies to prevent, identify, and manage symptoms of HIV-associated non-AIDS conditions and other comorbidities among older adults with prolonged HIV infection.[1683]

Although combination ART has been shown to prevent or delay the progression of HAND, a large portion of people with HIV are affected by a mild form of HAND.[1684] A study supported by NIA and OAR evaluated approximately 400 men with HIV ages 50 and older enrolled in the Multicenter AIDS Cohort Study (MACS)—the longest-running HIV cohort study in the world, which prospectively follows thousands of homosexual and bisexual men (with and at risk for HIV) across multiple sites. During the study, participants underwent MRI scanning at two-year intervals and neuropsychological testing to measure HIV- and age-associated cognitive impairments. Results, published in 2018, indicate that researchers found that participants' cognitive performance patterns did not link directly to HIV serostatus—the detectable presence, or lack thereof, of HIV antibodies.[1685,1686] Additionally, older individuals or those who use alcohol or substances can be at higher risk for developing HAND.[1687] In 2018, NIDA awarded funding to support research aimed at providing insight into the progression of HAND in people with HIV and possible options for preventing or treating HAND.[1688] In 2017, NIDA-supported researchers published results from another study that indicated that an adaptive working memory training program improved cognitive performance in participants with HIV.[1689] The research sheds light on how HIV-induced cognitive-performance declines, which can lead to HAND, can be reversed with cognitive intervention.

Malaria

Despite significant gains toward control and elimination of malaria, the mosquito-borne disease remains a significant public health problem, with almost half of the world's population at risk.[1690] In 2017, 87 countries recorded ongoing transmission, and an estimated 219 million cases and 435,000 deaths due to malaria were reported worldwide.[1691] NIH continues its long-standing commitment to malaria research,

[1681] https://grants.nih.gov/grants/guide/pa-files/PA-18-143.html.
[1682] https://grants.nih.gov/grants/guide/pa-files/PA-18-143.html.
[1683] https://grants.nih.gov/grants/guide/pa-files/PA-18-143.html.
[1684] https://www.nimh.nih.gov/health/topics/hiv-aids/index.shtml.
[1685] Molsberry S, et al. *AIDS* 2018;32(12):1679-88. PMID: 29762177.
[1686] https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/1632/serostatus.
[1687] https://projectreporter.nih.gov/project_info_description.cfm?aid=9088433&icde=46663789.
[1688] https://projectreporter.nih.gov/project_info_description.cfm?aid=9484263&icde=46663408.
[1689] Chang L, et al. *Ann Neurol* 2017; 81(1):17-34. PMID: 27761943.
[1690] https://www.who.int/news-room/fact-sheets/detail/malaria.
[1691] https://www.who.int/news-room/fact-sheets/detail/malaria.

allocating $183 million in FY 2016, $192 million in FY 2017, and $202 million in FY 2018 toward conducting and supporting research.[1692]

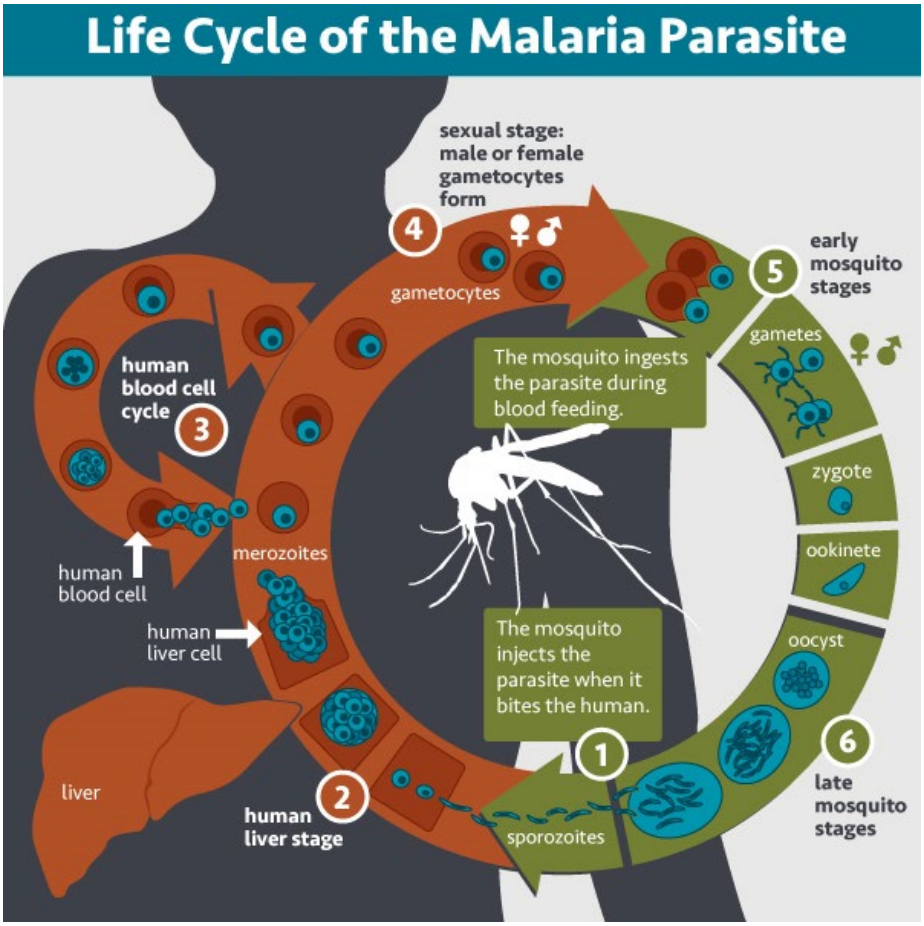

Figure 88. An illustration of the life cycle of the malaria parasite. Credit: NIAID.

Novel approaches and tools are needed to expand crucial malaria prevention, control, and eradication efforts. NICHD intramural researchers may have solved a long-standing mystery of why iron supplements can sometimes worsen malaria infection. They found that extra iron interferes with ferroportin, a protein that prevents a toxic buildup of iron in red blood cells and helps protect these cells against malaria infection.[1693] They also found that a mutant form of ferroportin that occurs in African populations appears to protect against malaria.[1694] These findings may help researchers and health care officials develop strategies to prevent and treat malaria infections.

[1692] https://report.nih.gov/categorical_spending.aspx.
[1693] https://www.nichd.nih.gov/newsroom/news/032918-malaria.
[1694] Zhang D, et al. *Science* 2018;359(6383):1520-23. PMID: 29599243.

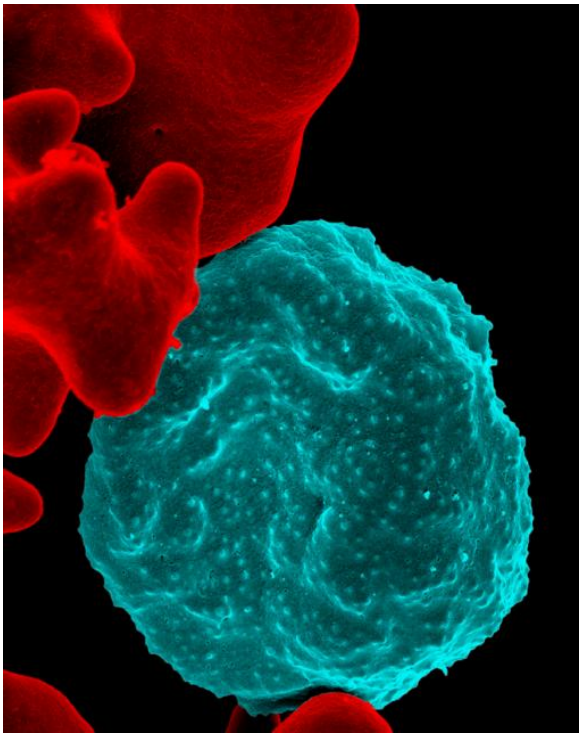

Figure 89. Colorized scanning electron micrograph of a red blood cell infected with malaria parasites, which are colorized in blue. The infected cell is in the center of the image area. To the left are uninfected cells with a smooth red surface. Credit: NIAID.

Researchers funded by NIBIB at the Massachusetts Institute of Technology have created a capsule that, when dissolved in the stomach, releases a star-shaped material containing drugs that help to prevent malaria infections and lasts for up to two weeks.[1695] This is particularly important given that a large portion of the at-risk population lives in rural areas, where access to doctors can be a challenge, which means that many patients often do not comply with the strict daily schedule that malaria-prevention medicines require.[1696] This long-lasting drug delivery system could eventually eliminate the need to take daily medication and help decrease the spread of malaria.

Additionally, NIH intramural and extramural investigators supported by NCI, NIAID, and NIGMS isolated the antibody CIS43 from the blood of a volunteer who had received the experimental vaccine (PfSPZ Vaccine-Sanaria) made from whole, weakened malaria parasites. Using two different models of malaria infection in mice, the researchers discovered that the antibody was highly effective at preventing malaria infection.[1697] The research findings provide the basis for future testing in humans to determine whether the antibody can provide short-term protection against malaria and may aid in vaccine design. Such a

[1695] Bellinger A, et al. *Sci Transl Med* 2016;8(365):365ra157.
[1696] https://www.nibib.nih.gov/news-events/newsroom/long-lasting-drug-delivery-system-may-help-decrease-spread-malaria.
[1697] Kisalu NK, et al. *Nat Med* 2018;24(4):408-16. PMID: 29554083.

prophylactic antibody could be useful for tourists, health care workers, military personnel, or others who travel to areas where malaria is common.[1698]

Figure 90. Doorway to a NIAID lab that conducts research on mosquitoes, insect vectors, and vector-borne infectious diseases. Credit: NIAID.

Three small Phase I clinical trials, supported by NIAID, investigated the PfSPZ Vaccine—a malaria vaccine containing weakened malaria parasites that do not cause infection but are able to generate a protective immune response against a live malaria infection. In one trial, the vaccine protected a significant portion of healthy adults against *Plasmodium falciparum* malaria for the duration of malaria season.[1699] In a second Phase I trial, the vaccine protected healthy adults against a malaria strain different from that contained in the vaccine.[1700] In the third study, the vaccine was incorporated with the antimalaria medication chloroquine in a vaccine strategy known as PfSPZ-CVac. The strategy protected all nine clinical trial volunteers given three high-dose vaccinations in a controlled infection setting.[1701] The results from

[1698] https://www.niaid.nih.gov/news-events/newly-described-human-antibody-prevents-malaria-mice.
[1699] https://www.niaid.nih.gov/news-events/investigational-pfspz-malaria-vaccine-demonstrates-considerable-protection-malian-adults.
[1700] https://www.niaid.nih.gov/news-events/experimental-pfspz-malaria-vaccine-provides-durable-protection-against-multiple-0.
[1701] https://www.niaid.nih.gov/news-events/experimental-malaria-vaccine-plus-chloroquine-protects-against-controlled-infection.

these trials could lead to a licensed vaccine against malaria, which does not currently exist, providing a critical tool in malaria prevention efforts.

Mosquitos continue to be the main target for prevention and control of malaria. Using genetically modified (GM) mosquitoes to reduce or prevent the spread of infectious diseases is a new, but rapidly expanding, field of investigation. NIAID-funded investigators engineered GM mosquitoes to have an altered microbiota that suppresses human malaria–causing parasites.[1702] The GM mosquitoes preferred to mate with wild mosquitoes and passed along the desired protection to many generations of offspring.[1703] The study suggests that mosquitoes can be genetically modified to compete in nature with wild populations and spread resistance to the malaria-causing parasite. If implemented, this strategy could eventually result in decreased disease transmission to humans.[1704]

To improve malaria diagnostics, which still relies on microscopes to analyze blood smears, NLM is collaborating with NIAID's Laboratory of Malaria and Vector Research and others to develop a fully automated system for parasite detection and counting in blood films. The system uses novel image processing and machine-learning algorithms to perform automatic parasite counting in thick and thin red blood smears, as well as digital images acquired on standard light microscopy equipment, which makes it well suited for resource-poor settings.[1705] NLM researchers developed a highly reliable deep-learning algorithm that screens for malaria with 99 percent accuracy by detecting the presence of the malaria-causing parasite in red blood cell images. The algorithm, implemented in a smartphone, underwent successful field tests in low-resource areas and has broad applicability to abnormal blood cell recognition.

Tuberculosis

TB is the leading infectious cause of death worldwide, killing roughly 1.6 million people in 2017.[1706] TB, a disease caused by the bacterium *Mycobacterium tuberculosis* (*Mtb*), often affects the lungs of an infected individual, and not everyone infected with TB bacteria becomes sick. NIH-supported research has sought to identify new treatments, determine which patients can effectively be treated by existing treatments, and develop new tools and strategies to improve diagnosis. NIH devoted $290 million in FY 2016, $347 million in FY 2017, and $403 million in FY 2018 to TB research.[1707]

Building on current global research efforts, NIAID developed a strategic plan that outlines research priorities to further the understanding of TB and to develop and apply cutting-edge tools to fight the disease.[1708] The *NIAID Strategic Plan for Tuberculosis Research* prioritizes expanding fundamental knowledge of TB by using modern tools, such as state-of-the-art imaging and systems biology methods, to better ascertain how TB infection remains latent in some individuals and then progresses to active

[1702] https://www.niaid.nih.gov/news-events/disease-resistance-successfully-spread-modified-wild-mosquitoes.
[1703] Pike A, et al. *Science* 2017;357(6358):1396-9. PMID: 28963254.
[1704] https://www.niaid.nih.gov/news-events/disease-resistance-successfully-spread-modified-wild-mosquitoes.
[1705] https://ceb.nlm.nih.gov/projects/malaria-screener/.
[1706] https://www.niaid.nih.gov/diseases-conditions/tuberculosis.
[1707] https://report.nih.gov/categorical_spending.aspx.
[1708] Fauci A. *JAMA* 2018;320(13):1315-6. PMID: 30267054.

disease, as well as the host and microbial factors that affect TB disease, transmission, and epidemiology.[1709] The plan was released in 2018 and will help guide NIH's efforts to develop tools to improve diagnosis, prevention, and treatment of TB.

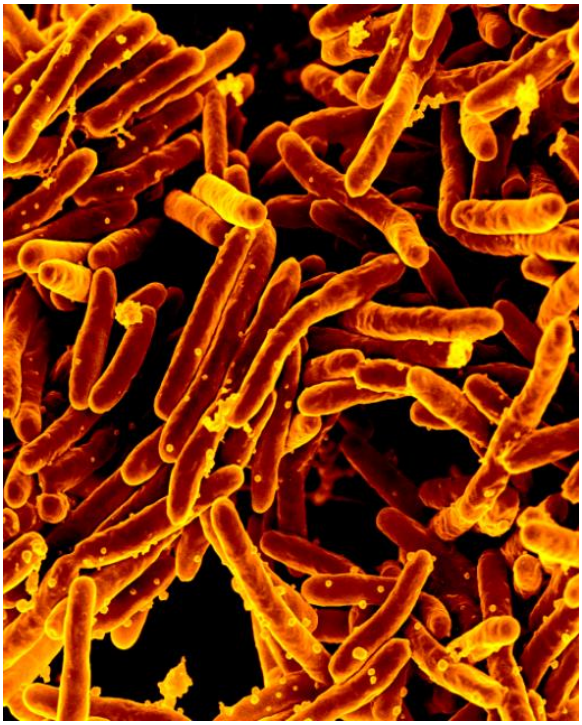

Figure 91. Scanning electron micrograph of *Mycobacterium tuberculosis* bacteria, which cause tuberculosis. Credit: NIAID

Although treatments exist for TB, drug resistance continues to be an issue necessitating improved treatment options. Since 2012, the NIH Oxford-Cambridge Scholars Program (OxCam) has enabled future scientists to work with NCATS researchers to explore the translation of promising new therapies for cancers and TB. An example of an NCATS translational research mentorship project is the development of chemical probes for studying human biology, using these compounds to "probe" the function of molecules, such as proteins, to understand their roles in health and disease.[1710] Through the NIH OxCam Program and mentorship of an NCATS intramural investigator, a doctoral student discovered a small molecule that was selective for the bacterial version of fumarate hydratase—a metabolic enzyme—but not the human version.[1711] Future work could lead to promising new TB drug candidates.

Although TB can often be treated through a long and grueling course of antibiotics, not everyone is completely cured. About 5 percent of patients relapse within six months of completing standard treatment, and predicting whether a patient will relapse can be difficult.[1712] In 2018, NIAID-supported researchers sought to determine if identifying the level of drug required to kill the *Mtb* strains in a new

[1709] https://www.niaid.nih.gov/news-events/niaid-releases-strategic-plan-address-tuberculosis-research.
[1710] https://ncats.nih.gov/pubs/features/oxcam-scholars.
[1711] https://ncats.nih.gov/chemtech/projects/active/tuberculosis.
[1712] https://www.niaid.nih.gov/news-events/tb-relapse-risk.

patient's sputum could predict whether the patient would relapse once treatment was complete.[1713] The researchers found that strains collected from volunteers who relapsed required higher concentrations of two TB drugs, isoniazid and rifampicin, to halt their growth, on average, as compared to strains collected from patients who were cured.[1714] Based on these results, researchers developed a model to predict how likely a patient with drug-susceptible TB will relapse. This has the potential to improve TB treatment success rates and decrease the development of drug-resistant *Mtb*.

For people with weakened immune systems, such as those with HIV infection, the risk of developing TB disease is much higher than for those with normal immune systems. A one-month antibiotic regimen to prevent active TB disease was at least as safe and effective as the standard nine-month therapy for people with HIV, according to results from a Phase III clinical trial sponsored by NIAID.[1715] Adults and adolescents in the trial were more likely to complete the short-course regimen (consisting of daily doses of the antibiotics for four weeks) than the standard nine-month regimen of daily isoniazid. Additionally, both preventive regimens were safe, with fewer adverse events occurring in the one-month treatment arm.[1716] Utilizing a short-course therapy could be an important tool to increase treatment adherence and control HIV-related TB.

Current treatment options for multidrug-resistant (MDR) TB require patients to take an injectable medication over the course of four to eight months.[1717] NICHD-supported researchers developed a way to make the treatment for MDR-TB effective and less painful for children and adolescents by administering the injections with lidocaine, a local anesthetic.[1718] The results have the potential to improve the tolerability of injectable treatment options without limiting the effectiveness.

NIH supports the development of new and improved diagnostic tools for faster and more accurate diagnosis of early TB disease and *Mtb* infection. NIAID has supported the development of a diagnostic test, called the Xpert MTB/RIF, to rapidly identify *Mtb*. The test is simple to use, and results can be provided in less than two hours, whereas traditional tests to determine drug resistance require weeks to generate results.[1719] NIAID-supported researchers conducted a prospective diagnostic accuracy study to learn how well the Xpert MTB/RIF test could identify *Mtb* mutations resistant to antibiotics used in TB treatment. The researchers found that the test was able to accurately detect drug resistance–associated mutations in several antibiotics commonly used to treat TB.[1720] The results, published in 2017, suggest the use of Xpert MTB/RIF could greatly impact the treatment of TB by detecting resistance earlier and faster.

[1713] https://www.niaid.nih.gov/news-events/tb-relapse-risk.
[1714] Colangeli R, et al. *N Engl J Med* 2018;379:823-33. PMID: 30157391.
[1715] https://www.niaid.nih.gov/news-events/one-month-tuberculosis-prophylaxis-effective-nine-month-regimen-people-living-hiv.
[1716] https://www.niaid.nih.gov/news-events/one-month-tuberculosis-prophylaxis-effective-nine-month-regimen-people-living-hiv.
[1717] https://europepmc.org/abstract/med/29561515.
[1718] https://europepmc.org/abstract/med/29561515.
[1719] https://www.niaid.nih.gov/research/antimicrobial-resistance-diagnosis.
[1720] Xie YL, et al. *N Engl J Med* 2017; 377(11):1043-54. PMID: 28902596.

NIH-supported researchers are also exploring innovative methods to detect TB in children. Current testing is invasive and time consuming, which can be problematic to implement in resource-limited settings. Using an SBIR grant awarded in 2016 by NICHD, researchers have set out to demonstrate the feasibility of rapid and sensitive detection of TB using novel technology in breath condensation, saliva, and urine samples.[1721] If successful, this project would provide a rapid, easy-to-use, and cost-effective point-of-care test, enabling routine early testing and screening of TB in children at home and in local community health care settings.[1722]

Viral Hepatitis

Hepatitis is an inflammation of the liver and is most commonly causes by viruses. At least five different hepatitis viruses (A, B, C, D, and E) are known to cause hepatitis. Hepatitis A and E typically cause acute infections, whereas hepatitis B, C, and D can cause both acute and chronic infections. Hepatitis B, C, and D afflict more than half a billion people worldwide and are responsible for more than a million deaths a year. Chronic infection with these viruses can lead to cirrhosis of the liver, end-stage liver disease, and liver cancer.[1723] Vaccines are available for hepatitis A and B; however, a vaccine is still not available for hepatitis C. Although treatment options are available for hepatitis A and chronic hepatitis C, treatment options are still lacking for hepatitis B, both acute and chronic infections, and acute hepatitis C. NIH funding for viral hepatitis research was $267 million in FY 2016, $306 million in FY 2017, and $349 million in FY 2018.[1724] NIH has supported research focusing on understanding the immune response to infection, the course of disease development, and developing new therapeutics for these viruses.

Hepatitis B Virus

An estimated 850,000 to 2.2 million people in the U.S. have chronic hepatitis B, with many unaware that they are infected.[1725] NIDDK continues to support projects conducted within the Hepatitis B Research Network (HBRN). This network aims to advance the understanding of disease processes and natural history of chronic hepatitis B virus (HBV) and to identify effective approaches to treatment with currently available therapies.[1726] Through public–private partnerships and collaboration with CDC, this multicenter network, with sites throughout the U.S. and Canada, conducted multiple clinical trials and ancillary studies involving both adults and children with HBV.[1727] The four studies, described below, utilized the HBRN to conduct large cohort studies of patients with chronic HBV and published their results between 2016 and 2018.

[1721] https://projectreporter.nih.gov/project_info_description.cfm?aid=9255903&icde=43405728.
[1722] https://projectreporter.nih.gov/project_info_description.cfm?aid=9255903&icde=43405728.
[1723] https://www.niaid.nih.gov/diseases-conditions/hepatitis.
[1724] https://report.nih.gov/categorical_spending.aspx.
[1725] https://www.niddk.nih.gov/health-information/liver-disease/viral-hepatitis/hepatitis-b.
[1726] https://www.hepbnet.org/.
[1727] https://www.hepbnet.org/.

For patients with chronic hepatitis, fatigue is a common symptom and has been shown to impact patients' quality of life; however, the association between fatigue and chronic HBV in patients is not well understood.[1728] Researchers found that higher fatigue rates were reported in patients with chronic HBV compared with the general U.S. population and were often associated with advanced liver disease.[1729] To better characterize chronic HBV in U.S.-born and foreign-born African American patients, groups in which HBV is highly prevalent, one study evaluated 237 African Americans enrolled in the HBRN.[1730] Their results emphasize the importance of tailored prevention, treatment, and management strategies for this patient population.[1731]

In 2017, researchers reported on their analysis of more than 1,500 patients enrolled in the HBRN. The study aimed to determine whether a link exists between liver disease and metabolic syndrome, a group of risk factors that increases risk for heart disease and other health problems.[1732,1733] The results indicated that metabolic syndrome is highly prevalent in patients with chronic HBV; these findings have implications for screening and treating HBV patients.[1734] Finally, to verify the phases or stages commonly used to characterize chronic HBV, researchers developed a computer algorithm to assess the phenotype of hepatitis B.[1735] Analysis of 1,390 adult patients enrolled in the HBRN indicated that 38 percent did not fit into any one phase/stage.[1736] The results could affect how clinicians characterize disease in chronic HBV patients.

Hepatitis C Virus

Several newer medicines, called direct-acting antiviral (DAA) medicines, have been approved to treat hepatitis C virus (HCV) since 2013. In 2017, NIDDK supported an investigator-initiated study analyzing the impacts of DAA drugs to treat HCV infection in terms of how many people with decompensated cirrhosis—compromised liver function associated with clinical complications—from HCV infection were wait-listed for a liver transplant. The researchers showed that the rate of liver transplant wait-listing in this patient population went down by more than 30 percent with the availability of these more effective drugs.[1737] The researchers think that with continued testing, access to care, and treatment using DAA medicines, additional reductions in liver transplant wait-listing for this group could be anticipated in the future.[1738]

[1728] Evon D, et al. *Dig Dis Sci* 2016; 61(4): 1186-96. PMID: 26831489.
[1729] Evon D, et al. *Dig Dis Sci* 2016; 61(4): 1186-96. PMID: 26831489.
[1730] Hassan M, et al. *Am J Epidemiol* 2017; 186(3): 356-66. PMID: 28525625.
[1731] Hassan M, et al. *Am J Epidemiol* 2017; 186(3): 356-66. PMID: 28525625.
[1732] Khalili M, et al. *Diabetes Care* 2018; 41(6): 1251-9. PMID: 29599296.
[1733] https://www.nhlbi.nih.gov/health-topics/metabolic-syndrome.
[1734] Khalili M, et al. *Diabetes Care* 2018;41(6):1251-9. PMID: 29599296.
[1735] Di Bisceglie A, et al. *J Viral Hepat* 2017;24(4):320-9. PMID: 27917600.
[1736] Di Bisceglie A, et al. *J Viral Hepat* 2017;24(4):320-9. PMID: 27917600.
[1737] Flemming JA, et al. *Hepatology* 2017;65(3):804-12. PMID: 28012259.
[1738] Flemming JA, et al. *Hepatology* 2017;65(3):804-12. PMID: 28012259.

Hepatitis D Virus

Currently, treatment for hepatitis D virus (HDV) is not considered very effective and can last 48 weeks.[1739] In 2016, a pilot clinical trial conducted by scientists in the NIDDK IRP, in collaboration with an international group of investigators and the drug sponsor, provided the first evidence that a drug called lonafarnib may be safe and effective as the only dedicated treatment available for chronic hepatitis D.[1740] This first human trial showed the promise of lonafarnib as a potentially groundbreaking new type of therapy for chronic hepatitis D. In another trial to optimize use of lonafarnib, researchers compared five different treatment regimens with lonafarnib, alone and in combination with other antiviral drugs, that showed promising results—particularly with the combination therapies.[1741] Future studies will continue to explore long-term therapy, dose adjustment, and combination with drugs to increase the antiviral activity and reduce side effects of treatment.

Other Major Infectious Diseases

In addition to HIV/AIDS, malaria, TB, and viral hepatitis, NIH supports research on many other major infectious diseases, several of which are outlined here.

Herpes Simplex Virus

Herpes simplex virus (HSV-1) infection of the eye remains a leading cause of infectious agent–induced blindness. Most existing antiviral drugs inhibit DNA replication to prevent the spread of the infectious agent in patients, but patients have no second line of defense if the virus develops resistance to the treatment. NEI-funded researchers reported in 2018 that the drug candidate BX795 works to inhibit ocular HSV-1 infection by inhibiting protein synthesis.[1742] Researchers are currently testing whether this mechanism of action is specific to HSV-1 or if it can be applied to other viruses, such as HIV. NIAMS intramural scientists examined the cellular processes involved in the maturation of HSV-1 inside a host cell before the virus is released to infect neighboring cells. They reported in 2017 the identification of a unique process that key viral proteins must undergo to move through the cell, revealing several potential therapeutic targets.[1743]

Varicella-Zoster virus

Varicella-zoster virus (VZV)—the virus that causes chickenpox, a common childhood disease—is now vaccinated against early in life. However, once a patient is infected, the virus can lay dormant for the duration of patients' lives. When reactivated, the virus causes shingles, known in the eye as herpes zoster ophthalmicus (HZO), and can lead to blindness. The Zoster Eye Disease Study, supported in part by NEI, is a 5-year clinical trial involving 60 medical centers. Launched in 2017, the study will investigate the

[1739] https://www.who.int/news-room/fact-sheets/detail/hepatitis-d.
[1740] Koh C, et al. *Lancet Infect Dis* 2015;15(10): 1167-1174. PMID: 26189433.
[1741] Yurdaydin C, et al. *Hepatology* 2017;67(4): 1224-1236. PMID: 29152762.
[1742] Jaishankar D, et al. *Sci Transl Med* 2018;10(428): eaan5861. PMID: 29444978.
[1743] Newcomb W, et al. *mBio* 2017;8(3):e00825-17. PMID: 28611252.

effectiveness of long-term low dosing of the antiviral agent valacyclovir in reducing complications of HZO.[1744]

Respiratory Syncytial Virus

A common virus, respiratory syncytial virus (RSV) typically causes mild, cold-like symptoms that resolve within two weeks; however, the virus can cause severe symptoms, especially among infants and young children.[1745] In the U.S., nearly all children become infected with RSV by age 2, with 75,000–125,000 of them hospitalized each year.[1746] Currently, no vaccine to prevent RSV infection or drug to treat it is available. In 2017 and 2018, NIAID launched two Phase I clinical trials of investigational vaccines designed to protect against RSV. The first vaccine candidate is a single structurally engineered protein from the surface of RSV, rather than a more traditional approach based on a weakened or inactivated whole virus.[1747] The study is enrolling healthy adults ages 18–50 years and is testing three different doses of the vaccine.[1748] The second study is enrolling a small group of healthy adult volunteers to examine the safety and efficacy of an experimental intranasal vaccine against RSV and assess the vaccine's ability to prompt an immune response.[1749]

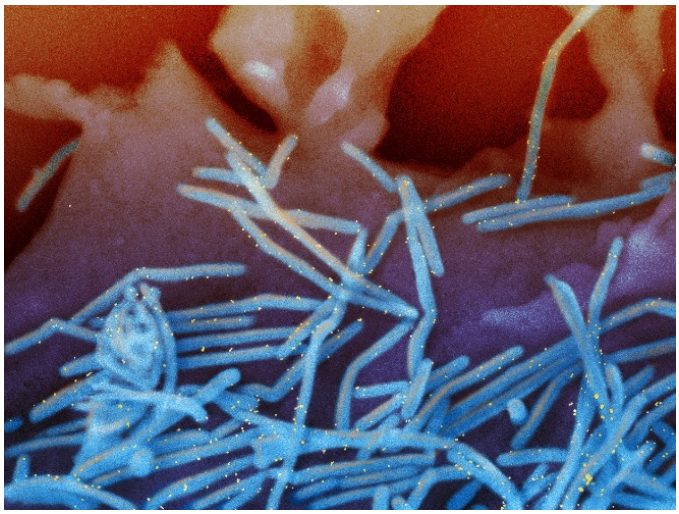

Figure 92. Scanning electron micrograph of human respiratory syncytial virus (RSV) virions (colorized blue) and labeled with anti-RSV F protein/gold antibodies (colorized yellow) shedding from the surface of human lung epithelial A549 cells. Credit: NIAID.

[1744] https://clinicaltrials.gov/ct2/show/NCT03134196.
[1745] https://www.niaid.nih.gov/news-events/early-stage-respiratory-syncytial-virus-rsv-vaccine-trial-begins.
[1746] https://www.niaid.nih.gov/news-events/early-stage-respiratory-syncytial-virus-rsv-vaccine-trial-begins.
[1747] https://www.niaid.nih.gov/news-events/respiratory-syncytial-virus-vaccine-enters-clinical-testing.
[1748] https://www.niaid.nih.gov/news-events/respiratory-syncytial-virus-vaccine-enters-clinical-testing.
[1749] https://www.niaid.nih.gov/news-events/early-stage-respiratory-syncytial-virus-rsv-vaccine-trial-begins.

Tickborne Disease

Tickborne infections have increased significantly in the U.S. within the past decade.[1750] Ticks can transmit at least 19 types of bacteria, viruses, and protozoa known to cause Lyme disease, Rocky Mountain spotted fever, tularemia, and a host of other potentially serious illnesses.[1751] If a tick becomes attached to a person's skin, no quick way currently exists to determine whether they have been exposed to a pathogen and, if so, which specific ones. A 2018 paper in *Scientific Reports* describes the NIAID-supported Tickborne Disease (TBD) Serochip that, using a single sample of blood, can simultaneously detect and distinguish among antibodies associated with exposure to eight common tickborne pathogens.[1752] The TBD Serochip is also able to identify whether a person had been infected by more than one tickborne pathogen.[1753] The data suggest the TBD Serochip could be a promising addition to TBD diagnostics.

Figure 93. A male adult dog tick, or *Dermacentor variabilis,* crawls over a penny. Dog ticks can transmit pathogens that cause tickborne diseases, such as Rocky Mountain spotted fever and tularemia. Credit: NIAID.

The Common Cold

NIH continues to support research to better understand respiratory viral infections and the common cold—one of the most common illnesses, with more than 200 different viruses known to cause the symptoms of the common cold.[1754] NIAID scientists discovered a rare genetic mutation that results in a markedly increased susceptibility to infection by human rhinoviruses—the main causes of the common cold.[1755] Researchers at NIAID identified the mutation in a young child with a history of severe rhinovirus infections. The analysis revealed that the child had a mutation in the *IFIH1* gene that caused her body to make dysfunctional MDA5 proteins—which are critical to recognizing and triggering an immune response

[1750] https://www.niaid.nih.gov/diseases-conditions/tickborne-diseases.
[1751] https://directorsblog.nih.gov/2018/06/26/precision-diagnosis-for-tick-borne-diseases/.
[1752] https://directorsblog.nih.gov/2018/06/26/precision-diagnosis-for-tick-borne-diseases/.
[1753] Tokarz R, et al. *Sci Rep* 2018;8(1):3158. PMID: 29453420.
[1754] https://www.nih.gov/news-events/nih-research-matters/understanding-common-cold-virus.
[1755] https://www.niaid.nih.gov/news-events/niaid-scientists-discover-rare-genetic-susceptibility-common-cold.

against rhinoviruses—in cells in her respiratory tract.[1756] Insights from the study may one day lead to new strategies for treating patients with severe rhinovirus complications. NIAID-supported researchers also analyzed genetic data from 18 publicly available datasets to identify host factors necessary for susceptibility or resistance to respiratory infection.[1757] The researchers identified a genetic signature common across different respiratory viral infections, which allowed them to distinguish people with viral infections from healthy individuals and from people with bacterial infections.[1758] By further analyzing the signatures, researchers could also detect virally infected people prior to the onset of symptoms.[1759] The results could inform future diagnostic and treatment options.

NIH has also explored how herbs may have potential health affects against infectious diseases. For example, results of a 2016 study add to the growing body of literature suggesting that differences in the bacteria inside echinacea plants may determine whether and how much the herb contributes to enhancing the immune system and fighting infectious diseases like the common cold.[1760] Both the types of bacteria and the quantity of bacteria within the plants may contribute to differences in their effects. The study, supported by NCCIH, was published in *Planta Medica* and awarded Most Innovative Paper of the Year (2016) by journal editors.

Sepsis

NIH-supported research has led to discoveries of potentially lifesaving, low-cost treatments and prevention strategies for sepsis—a life-threatening condition in which the body's immune system produces an extreme response to an infection. NIH-funded researchers demonstrated in preclinical studies that high-dose vitamin C improved survival, reduced inflammation, and led to better lung function after sepsis in mice.[1761] Support from NCATS' CTSA program helped streamline translation of this promising therapy to multisite clinical studies to test the effectiveness of high doses of intravenous vitamin C.[1762] Another study, supported by NICHD, demonstrated that newborns who received daily oral doses of beneficial bacteria, which cost less than $1 a week, had lower rates of sepsis and, surprisingly, lower rates of pneumonia and other airway infections.[1763] This study is the first to show that probiotics therapy can prevent disease on a large scale, suggesting a cost-effective way to reduce a serious, widespread infection among newborns in developing countries. [1764] Results from both studies have the potential to reduce the impact of sepsis globally.

[1756] Lamborn IT, et al. *J Exp Med* 2017;214(7):1949-72. PMID 28606988.
[1757] Andres-Terre M, et al. *Immunity* 2015;43(6):1199-1211. PMID: 26682989.
[1758] Andres-Terre M, et al. *Immunity* 2015;43(6):1199-1211. PMID: 26682989.
[1759] Andres-Terre M, et al. *Immunity* 2015;43(6):1199-1211. PMID: 26682989.
[1760] Haron MH, et al. *Planta Med* 2016;82(14):1258-65. PMID: 27286330.
[1761] https://ncats.nih.gov/pubs/features/vcu-ctsa.
[1762] https://ncats.nih.gov/pubs/features/vcu-ctsa.
[1763] Panigrahi P, et al. *Nature* 2017; 548:407-12. PMID: 28813414.
[1764] https://www.nichd.nih.gov/newsroom/releases/082817-probiotics.

Emerging Infectious Diseases and Biodefense (Including Seasonal and Pandemic Influenza)

Emerging and re-emerging diseases and threats—such as influenza, Ebola, Zika, and AMR—significantly impact health in the U.S. and worldwide. NIH is the lead agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. Regardless of the source of the infectious threat, naturally occurring or manmade, NIAID's research approach is the same: Learn as much as possible about the infectious agent and how it causes disease, and develop tools to diagnose, treat, and prevent infection with that microbe.[1765]

Influenza

Influenza viruses continually change, can be easily transmitted from person to person, and have the potential to spread widely through communities, making seasonal and pandemic influenza a continual threat. The limitations of vaccines and treatments add another element to the challenge. Since 2010, CDC estimates that 9.3 million to 49.0 million illnesses have resulted from influenza in the U.S.[1766] The NIH is actively engaged in influenza research, including improving current vaccines and developing a universal vaccine. NIH devoted $263 million in FY 2016, $301 million in FY 2017, and $430 million in FY 2018 to influenza research.[1767]

Currently, seasonal influenza vaccines are designed to induce high levels of protective antibodies against hemagglutinin (HA)—a protein found on the surface of the influenza virus that is made up of a head, which varies season to season, and a stem, which typically remains unchanged.[1768] Higher levels of HA antibodies in a person's body have long been associated with greater protection against influenza infection and have traditionally been used to infer how effective the seasonal influenza vaccine might be against circulating viruses.[1769] However, variability in in seasonal influenza vaccine effectiveness has led researchers to consider other factors to improve vaccine performance.

[1765] https://www.niaid.nih.gov/research/biodefense-emerging-infectious-diseases-research.
[1766] https://www.cdc.gov/flu/about/burden/index.html.
[1767] https://report.nih.gov/categorical_spending.aspx.
[1768] https://www.niaid.nih.gov/diseases-conditions/universal-influenza-vaccine-research.
[1769] https://www.niaid.nih.gov/news-events/nih-study-finds-factors-may-influence-influenza-vaccine-effectiveness.

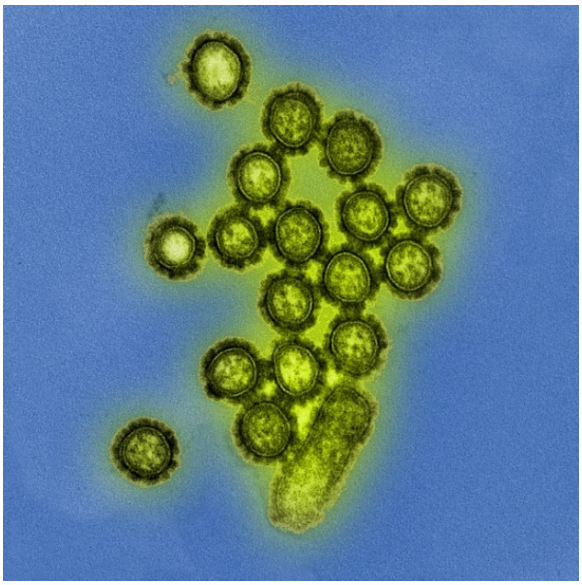

Figure 94. Colorized transmission electron micrograph showing H1N1 influenza virus particles. Surface proteins on the virus particles are shown in black. Credit: NIAID.

After exposing healthy volunteers to the 2009 H1N1 influenza virus under carefully controlled conditions, NIAID scientists observed that antibodies against a different influenza surface protein—neuraminidase (NA)—were the better predictor of protection against influenza infection and severity of illness.[1770] The data, published in 2016, suggest that NA antibodies may be the stronger factor for determining disease severity, and the role of NA antigens should also be considered for development of future influenza vaccine platforms.[1771] In another study, NIAID-funded scientists evaluated immune responses to the 2009 H1N1 influenza virus. They found that people with low levels of preexisting H1N1 influenza virus–specific antibodies generated neutralizing antibodies targeting the stalk region of HA, whereas those with higher levels of preexisting antibodies generated antibodies targeting the head region of HA.[1772] The investigators also noted that preexisting anti-head antibodies prevented clear access to the stalk by anti-stalk antibodies.[1773] The data suggest that considering immune history will be critical in the design of a universal flu vaccine that targets a wide variety of influenza strains.

Building on previous NA studies, a team of scientists—including investigators from the Centers of Excellence for Influenza Research and Surveillance program, which is organized and funded by NIAID—analyzed blood samples from people vaccinated against influenza and people diagnosed with either the 2009 H1N1 or H3N2 influenza viruses.[1774] Their analyses indicate that influenza vaccines rarely induce NA-reactive antibodies, whereas natural influenza infection induces these types of antibodies at least as often as they induce HA-reactive antibodies.[1775] Studies in mice reinforced the human data, indicating that

[1770] Memoli M, et al. *mBio* 2016;7(2):e00417-16. PMID: 27094330.
[1771] https://www.niaid.nih.gov/news-events/nih-study-finds-factors-may-influence-influenza-vaccine-effectiveness.
[1772] Andrews S, et al. *Sci Transl Med* 2015;7(316):316ra192. PMID: 26631631.
[1773] Andrews S, et al. *Sci Transl Med* 2015;7(316):316ra192. PMID: 26631631.
[1774] https://www.niaid.nih.gov/news-events/research-offers-clues-improved-influenza-vaccine-design.
[1775] Chen YQ, et al. *Cell* 2018; 173(2):417-29. PMID: 29625056.

current influenza vaccines do not induce NA-reactive antibodies efficiently.[1776] Additional laboratory experiments showed that the NA-reactive antibodies induced during natural influenza infection are broadly reactive, meaning they could potentially protect against diverse strains of influenza.[1777] These findings suggest that influenza vaccines should be optimized to better target NA for broad protection against diverse influenza strains.

Multiple factors impact the effectiveness of influenza vaccines, such as an individual's history of exposure to prior influenza viruses and vaccinations, age, genetics, and coexisting health problems. NIAID-supported research published in 2017 found that manufacturing strategies may also play a significant role in vaccine effectiveness.[1778] Currently, most influenza vaccines in the U.S. are produced using chicken eggs, although a few are made in cell culture or by using recombinant DNA technologies. The study suggests that mutations occurring in egg-prepared vaccines may have contributed to decreased vaccine effectiveness during the 2016–2017 influenza season in the U.S. and the 2017 flu season in Australia.[1779] The findings underscore the need for targeted research to further evaluate manufacturing strategies, vaccine antigens, and platforms to produce effective influenza vaccines.

Licensed influenza vaccines provide suboptimal protection against seasonal influenza, must be updated regularly to match circulating influenza strains, and offer little or no protection against newly emerged pandemic influenza strains.[1780] Thus, a key public health goal is to develop a universal influenza vaccine—a vaccine that can provide durable protection for all age groups against multiple influenza strains, including those that might cause a pandemic. In June 2017, NIAID held a workshop, *Pathway to a Universal Influenza Vaccine*, that brought together U.S. and international experts from academia, industry, and government to identify knowledge gaps in influenza research and to set goals to fill these knowledge gaps.[1781] The workshop report, published in the October 2017 issue of *Immunity*, was used by NIAID to develop a strategic plan and research agenda aimed at the development of a universal influenza vaccine.

In February 2018, NIAID released its *Universal Influenza Vaccine Strategic Plan* outlining the Institute's research priorities to address the research areas essential to creating a safe and effective universal influenza vaccine.[1782] In a *Journal of Infectious Diseases* article, NIAID officials detailed the Institute's new strategic plan, emphasizing that a coordinated effort of guided discovery, facilitated product development, and managed progress through iterative clinical testing will be critical to achieving the goal of a universal influenza vaccine.[1783] NIAID intends the plan to serve as the foundation for its research investment strategy to achieve this important public health goal.

[1776] https://www.niaid.nih.gov/news-events/research-offers-clues-improved-influenza-vaccine-design.
[1777] https://www.niaid.nih.gov/news-events/research-offers-clues-improved-influenza-vaccine-design.
[1778] https://www.niaid.nih.gov/news-events/fighting-flu-year-after-year.
[1779] Zost SJ, et al. *Proc Natl Acad Sci USA* 2017;114(47):12578-83. PMID: 29109276.
[1780] https://www.niaid.nih.gov/news-events/experts-outline-pathway-universal-influenza-vaccine.
[1781] https://www.niaid.nih.gov/news-events/experts-outline-pathway-universal-influenza-vaccine.
[1782] https://www.niaid.nih.gov/diseases-conditions/universal-influenza-vaccine-research.
[1783] https://www.niaid.nih.gov/news-events/niaid-unveils-strategic-plan-developing-universal-influenza-vaccine.

In 2018, a Phase II clinical trial of an investigational universal influenza vaccine intended to protect against multiple strains of the virus began in the U.S. Sponsored by NIAID, the study is being conducted at four U.S. sites that are part of the NIAID-funded Vaccine and Treatment Evaluation Units. The trial is testing the experimental vaccine, called M-001, for safety and its ability to produce potentially broad protective immune responses both on its own and when followed by a standard, licensed seasonal influenza vaccine.[1784] The trial will provide critical information that will inform development efforts of a universal influenza vaccine.

Ebola Virus Disease

Ebola virus disease (EVD), first recognized in 1976 in the Democratic Republic of the Congo (DRC), is a serious and often fatal illness in humans and nonhuman primates. The largest outbreak of Ebola occurred in 2014–2016 in West Africa—a region with no recognized prior Ebola outbreaks—and caused more than 28,600 infections and more than 11,300 deaths, according to the WHO.[1785] No licensed treatments are currently available for EVD, although multiple experimental therapies are being developed. NIH continues to support research developing and testing vaccines and treatments. Additionally, many NIH grantees and partners play important roles in the Ebola response in affected countries.

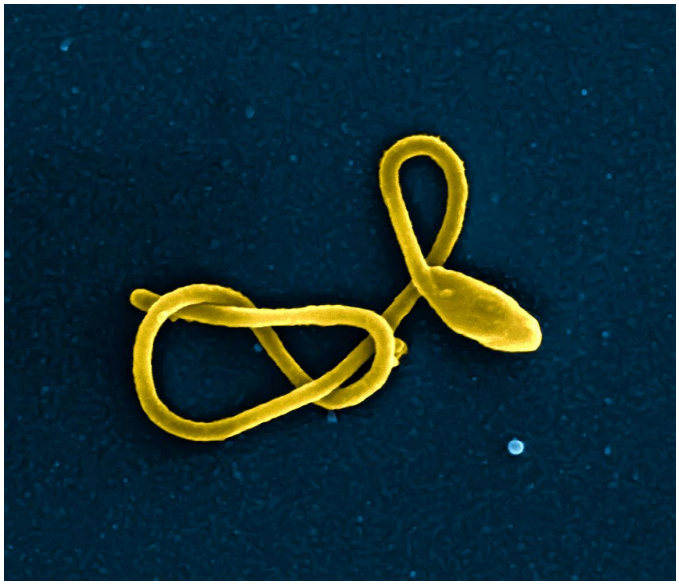

Figure 95. Scanning electron micrograph showing a single filamentous Ebola virus particle. Credit: NIAID.

Ebola virus (EBOV) causes a deadly infection, and surviving the initial infection is challenging; however, even after patients recover from the viral infection, they may be vulnerable to lingering health issues, such as vision loss. Invasive procedures to correct vision problems in EVD survivors, such as cataract surgery, are not recommended by the WHO, given the potential transmission risk. Researchers supported in part by NEI published results in 2018 from the Ebola Virus Persistence in Ocular Tissues and Fluids study,

[1784] https://www.niaid.nih.gov/news-events/niaid-sponsored-trial-universal-influenza-vaccine-begins.
[1785] https://www.niaid.nih.gov/diseases-conditions/ebola-marburg.

which aimed to determine if EBOV remains in ocular fluid of EVD survivors and explore the safety, feasibility, and effectiveness of vision correction procedures in EVD survivors. They found that cataract surgery could be safely performed in EVD survivors who tested negative for EBOV in their ocular fluid.[1786] The results have the potential to impact clinical care for patients with vision problems due to EBOV.

NIH supports the development of several vaccine candidates against EBOV, for which a licensed vaccine does not currently exist. A two-vaccine regimen induced an immune response that persisted for approximately one year in healthy adult volunteers, according to results from a Phase I clinical trial published in a 2017 issue of the *Journal of the American Medical Association*.[1787] NIAID supported the development and testing of the experimental vaccines (Ad26.ZEBOV, developed by Janssen Vaccines and Prevention B.V., and MVA-BN-Filo, developed by Bavarian Nordic) beginning with early nonclinical stages and manufacturing process development.[1788] Another trial launched in 2017, which builds on these studies and will compare three experimental Ebola vaccination strategies that include the two investigational vaccines with placebo groups.[1789] The trial seeks to identify the vaccination regimens that hold the most promise to prevent or quickly control a future Ebola outbreak.

Preparedness in the face of infectious disease threats that require a rapid response can save countless lives and may even stop a disease outbreak from developing into a pandemic. In August 2018, the DRC declared its 10th outbreak of Ebola. The DRC and WHO are leading a global, coordinated response, for which NIH is providing several layers of support.[1790]

A first-in-human trial evaluating an experimental treatment for EVD developed by NIAID researchers in partnership with the U.S. Army Medical Research Institute of Infectious Diseases and the Defense Advanced Research Projects Agency began in 2018 at the NIH Clinical Center.[1791] The Phase I clinical trial is examining the safety and tolerability of a single monoclonal antibody called mAb114 that is based on an antibody isolated from a human survivor of the 1995 Ebola outbreak in Kikwit, DRC.[1792]

[1786] Shantha J, et al. *EBioMedicine* 2018; 30: 217-224. PMID: 29622497.
[1787] Winslow R, et al. *JAMA* 2017;317(10):1075-7.
[1788] https://www.niaid.nih.gov/news-events/experimental-ebola-vaccine-regimen-induced-durable-immune-response-study-finds.
[1789] https://www.niaid.nih.gov/news-events/ebola-new-trial-launched-west-africa-evaluate-three-vaccination-strategies.
[1790] https://www.niaid.nih.gov/news-events/niaid-responds-ebola-outbreak-democratic-republic-congo.
[1791] https://www.niaid.nih.gov/news-events/nih-begins-testing-ebola-treatment-early-stage-trial.
[1792] https://www.niaid.nih.gov/news-events/nih-begins-testing-ebola-treatment-early-stage-trial.

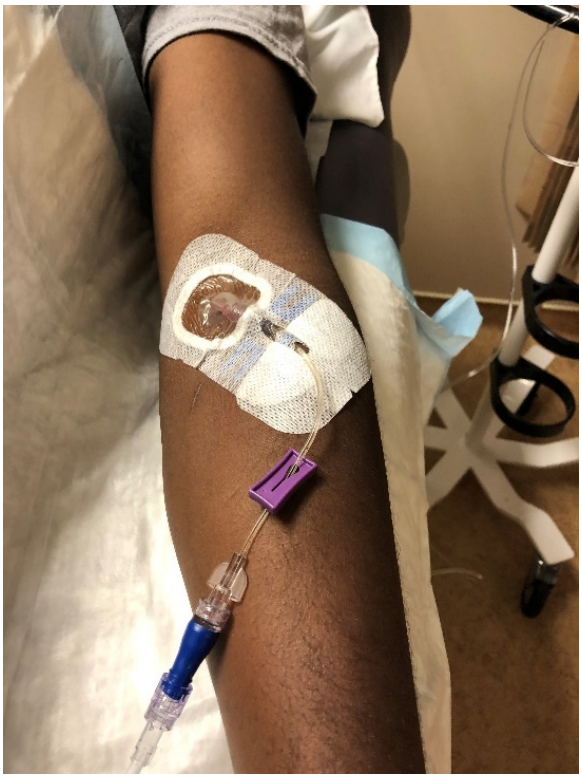

Figure 96. A healthy volunteer receives an intravenous infusion of mAb114—an experimental treatment for Ebola virus disease—in a Phase 1 clinical trial held in 2018 at the NIH Clinical Center in Bethesda, Maryland. Credit: NIAID.

An international research team began patient enrollment in November 2018 for an RCT testing multiple investigational Ebola therapies—including mAb114, ZMapp, and remdesivir—in the DRC. Led by the National Institute of Biomedical Research, part of the DRC Ministry of Health, and NIAID, the trial is enrolling patients of any age with confirmed EVD at a treatment unit in the city of Beni operated by The Alliance for International Medical Action, a medical humanitarian organization.[1793] The trial will evaluate the safety and efficacy of the investigational treatments. Hopefully, both trials will provide further insight into potential treatment options for Ebola patients.

NIAID is also providing emergency-use treatment courses of mAb114 and other investigational treatments under an ethical framework developed by the WHO called Monitored Emergency Use of Unregistered and Investigational Interventions.[1794] Taken together, these efforts promise to help mitigate the current Ebola outbreak and outbreaks that will inevitably emerge in the future.

[1793] https://www.niaid.nih.gov/news-events/clinical-trial-investigational-ebola-treatments-begins-democratic-republic-congo.
[1794] https://www.niaid.nih.gov/news-events/clinical-trial-investigational-ebola-treatments-begins-democratic-republic-congo.

Zika

In 2015, the Pan American Health Organization issued an alert regarding the first confirmed Zika virus (ZIKV) infection in Brazil. Since that time, ongoing ZIKV transmission has been reported throughout Central and South America, as well as the Caribbean.[1795] Cases of locally transmitted ZIKV in the continental U.S. were confirmed in 2016. ZIKV presents a new infectious threat, particularly to pregnant women and their fetuses, as ZIKV can be transmitted during pregnancy and result in serious birth defects.[1796]

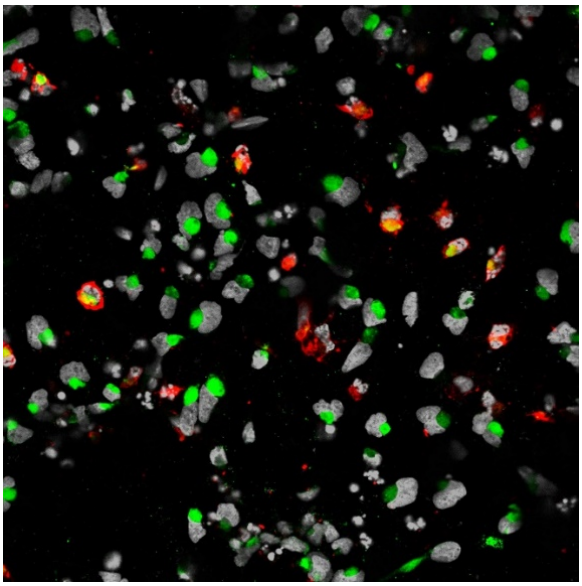

Figure 97. Neural cells infected with Zika virus. Credit: Sarah C. Ogden, Florida State University, Tallahassee, Florida.

The multicountry Zika in Infants and Pregnancy study, supported by NIAID, NICHD, NIEHS, and the Brazilian Fundacao Oswaldo Crus, the national research organization linked to the Brazilian Ministry of Health, was launched in 2016 to evaluate the extent of health risks that ZIKV infection poses to pregnant women and their developing fetuses and infants.[1797] The prospective observational cohort study aims to enroll up to 10,000 pregnant women in their first trimester at locations in Puerto Rico, Brazil, and Central America. The study is designed to follow the women throughout pregnancy and, along their infants, for at least a year after birth.[1798] Information from this study will help researchers further understand the full effect of ZIKV on pregnant women and their infants, thereby helping to inform treatment and prevention strategies.

To combat the growing threat, NIH has supported several clinical trials testing ZIKV vaccine candidates. In 2017, NIAID announced that vaccinations had begun in a multisite Phase II/IIb clinical trial testing an NIAID-developed experimental DNA vaccine designed to protect against disease caused by ZIKV infection.

[1795] https://www.niaid.nih.gov/diseases-conditions/zika-virus.
[1796] https://www.niaid.nih.gov/diseases-conditions/zika-virus.
[1797] https://www.niaid.nih.gov/news-events/nih-launches-large-study-pregnant-women-areas-affected-zika-virus.
[1798] https://www.nih.gov/news-events/news-releases/nih-launches-large-study-pregnant-women-areas-affected-zika-virus.

The vaccine was developed using a versatile vaccine platform approach that enabled moving from concept to clinical trial in less than 4 months during the 2015–2016 ZIKV outbreak. The NIAID-led trial aims to further evaluate the vaccine's safety and ability to stimulate an immune response and assess the optimal dose for administration.[1799] NIAID also partnered with the Walter Reed Army Institute of Research to co-fund Phase I clinical trials to test the investigational Zika vaccine candidate called the Zika Purified Inactivated Virus.[1800] Initial results published in 2018 indicated that the vaccine was well tolerated and induced an immune response in participants.[1801]

Research has also advanced knowledge of immune responses to ZIKV, which can help inform vaccine development. For example, in 2016, NIAID-funded scientists found that ZIKV infection confers protection against future infection in monkeys, suggesting that a vaccine that mimics natural immunity to ZIKV may be protective.[1802] They also found that the virus lingers in the bodies of pregnant monkeys for a prolonged time, and they are continuing to study the potential effects of this persistent infection.[1803] Another group of NIAID-supported researchers identified two antibodies that neutralized diverse ZIKV strains in Zika-infected mice.[1804] Mice given these antibodies as a preventive treatment developed lower blood levels of ZIKV and did not develop clinical signs of infection.[1805] The researchers also developed atomic-level structural images of the antibodies bound to a ZIKV protein—information that may aid vaccine development.

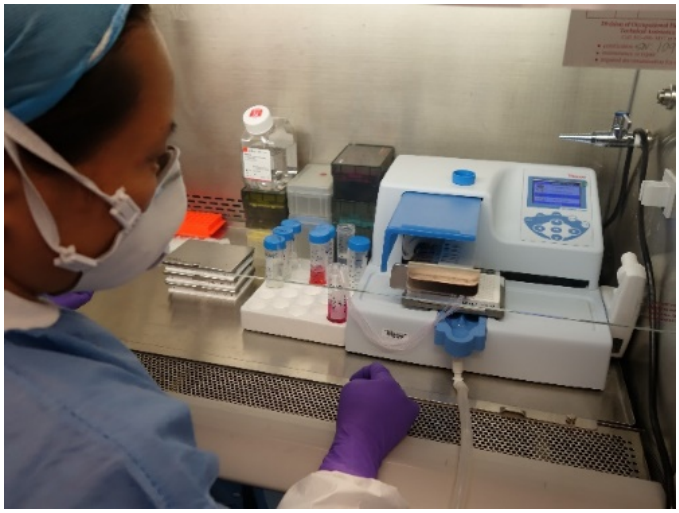

Figure 98. An NCATS researcher dispenses Zika virus into trays for compound screening in a lab using procedures that follow strict biosafety standards. Credit: NCATS.

[1799] https://www.niaid.nih.gov/news-events/phase-2-zika-vaccine-trial-begins-us-central-and-south-america.
[1800] https://www.niaid.nih.gov/diseases-conditions/zika-vaccines.
[1801] Modjarrad K, et al. *Lancet* 2018;391(10120):563-71. PMID: 29217375.
[1802] https://www.niaid.nih.gov/news-events/zika-virus-infection-may-be-prolonged-pregnancy.
[1803] Dudley D, et al. *Nat Commun* 2016;7:12204. PMID: 27352279.
[1804] https://www.niaid.nih.gov/news-events/studies-mice-provide-insights-antibody-zika-virus-interactions.
[1805] Zhao H, et al. *Cell* 2016;166(4):1016-27.

NIH continues to support multiple efforts toward developing treatment options for ZIKV infection, for which there is currently no specific treatment. NCATS investigators and extramural collaborators leveraged the NCATS drug repurposing program to screen thousands of potential drug candidates on Zika-infected human cells in a matter of weeks. The initial screen generated a list of compounds with potential promise for treating ZIKV infection, and the team was able to narrow the list down to lead candidates already used for other purposes but that appeared to affect ZIKV as well. NCATS' screening effort enabled the research team to quickly translate their earlier discoveries toward developing strong treatment candidates for ZIKV infection. This project demonstrates how NCATS' platforms can be nimble and flexible to be utilized for different diseases and emerging public health crises.[1806,1807]

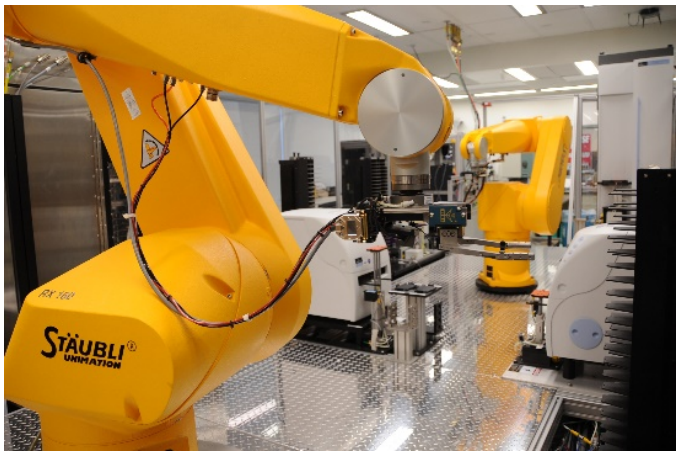

Figure 99. Automated robots help increase the speed and accuracy of the drug-screening process. Credit: NCATS

Using blood samples from an individual previously infected with ZIKV, scientists funded by NIAID have developed an antibody-based ZIKV therapeutic that protected monkeys from infection.[1808] The scientists isolated immune cells from the patient's blood and used them to make 91 monoclonal antibodies—immune system fighters designed to bind to a specific part of an invading virus or bacterium to stop the infection.[1809] Because monoclonal antibodies are generally safe, the scientists believe that this antibody cocktail might be appropriate for pregnant women who are not infected; because the antibodies will likely cross the placenta, the researchers hope that administration during pregnancy may protect both the pregnant woman and the fetus from Zika virus.[1810]

[1806] https://www.nih.gov/news-events/news-releases/nih-collaboration-helps-advance-potential-zika-treatments
[1807] Xu M, et al. *Nat Med* 2016;22(10):1101-7. PMID: 27571349.
[1808] https://www.niaid.nih.gov/news-events/monoclonal-antibodies-against-zika-show-promise-monkey-study.
[1809] https://www.niaid.nih.gov/news-events/monoclonal-antibodies-against-zika-show-promise-monkey-study.
[1810] https://www.niaid.nih.gov/news-events/monoclonal-antibodies-against-zika-show-promise-monkey-study.

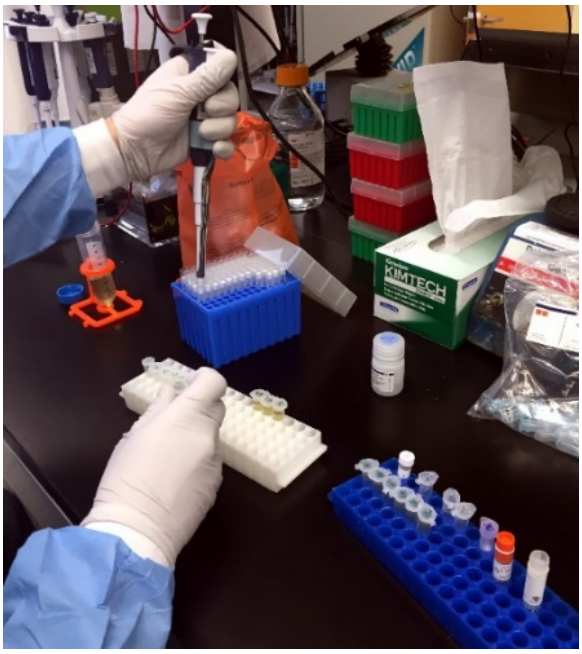

Figure 100. A Zika virus researcher at the NIAID Vaccine Research Center prepares samples. Credit: NIAID.

In another study, NIDCR-funded scientists have shown that ZIKV infects cranial neural crest cells, which are the cells that give rise to most of the tissues of the craniofacial region.[1811] ZIKV infection causes elevated levels of cytokines to be released, which may disrupt normal fetal development of cranial and facial structures.[1812] Knowledge from this study, published in 2016, has the potential to lead to treatments that will target these molecular pathways and prevent ZIKV-associated craniofacial abnormalities.

Zika infection has a known ocular component and has been associated with vision problems in infants born to mothers with ZIKV infection during pregnancy. Currently, no treatment is available to fully restore vision in babies with severe eye problems.[1813] NEI and NIAID supported researchers who examined 112 infants born to mothers with ZIKV infection during pregnancy and reported in 2017 that eye abnormalities could be an early manifestation of ZIKV disease in infants.[1814] The researchers recommended that all infants with possible exposure to the Zika virus undergo an eye examination.[1815]

Patient diagnosis during active infection with ZIKV is reliable, but serological diagnosis of infection after ZIKV can be difficult. Prior ZIKV can be detected by antibody-based tests; however, these tests may also detect or cross-react with antibodies against other flaviviruses, particularly dengue virus.[1816] NIAID-supported researchers established two assays that enable sensitive and specific diagnosis of ZIKV exposure. The new diagnostics enable differentiation of ZIKV infection against natural infection or

[1811] Bayless N, et al. *Cell Host Microbe* 2016;20(4):423-28. PMID: 27693308.
[1812] Bayless N, et al. *Cell Host Microbe* 2016;20(4):423-28. PMID: 27693308.
[1813] https://www.cdc.gov/pregnancy/zika/family/vision-problems-related-to-zika.html.
[1814] Zin A, et al. *JAMA Pediatr* 2017;171(9):847-54. PPMID: 28715527.
[1815] Zin A, et al. *JAMA Pediatr* 2017;171(9):847-54. PPMID: 28715527.
[1816] https://www.niaid.nih.gov/diseases-conditions/zika-diagnosis.

vaccination against dengue, chikungunya, yellow fever, and a number of other vector-borne illnesses after the viremic period of ZIKV infection has ended.[1817]

Other diagnostic development efforts include NIDCR-supported research to develop rapid, noninvasive, salivary diagnostics to improve ZIKV detection in pregnant women and other vulnerable individuals. One group of scientists is developing a point-of-care diagnostic device that works well in the field: It is inexpensive, small, and portable, and it runs on batteries.[1818] In another effort, a small business grant to adapt rapid HIV-detection technologies to ZIKV is supporting the development of a device capable of analyzing 24 samples simultaneously and with improved accuracy—detecting ZIKV RNA and proteins simultaneously.[1819]

Antimicrobial Resistance

Antimicrobials have been successfully used to treat patients with bacterial and infectious diseases for more than 70 years; over time, however, organisms have evolved and developed resistance to antimicrobials.[1820] In the U.S., antibiotic-resistant infections are responsible for at least 2 million illnesses and 23,000 deaths each year, according to CDC.[1821] NIH funding for AMR research was $420 million in FY 2016, $470 million in FY 2017, and $522 million in FY 2018.

NIH continues to support and conduct research to find new treatments effective against AMR organisms. Recently, NIAID-funded researchers discovered a new class of antibiotics called malacidins by analyzing the DNA of the bacteria living in more than 2,000 soil samples, including many sent by citizen scientists living all across the U.S.[1822] Although more work is needed before malacidins can be tried in humans, the compounds successfully killed several types of multidrug-resistant bacteria in laboratory tests.[1823] Most impressive was the ability of malacidins to wipe out Methicillin-Resistant *Staphylococcus aureus* (MRSA) skin infections in rats.[1824] Often referred to as a "super bug" due to its resistance to multiple antibiotics, MRSA threatens the lives of tens of thousands of Americans each year.

[1817] Mishra N, et al. *MBio* 2018; 9(2):e00095-18. PMID: 9511073.
[1818] Mauk M, et al. *Clin Lab Int* 2017;41:25-27. PMID: 28819345.
[1819] Sabalza M, et al. *PLoS ONE* 2018;13(2):e0192398. PMID:29401479.
[1820] https://www.niaid.nih.gov/research/antimicrobial-resistance.
[1821] https://www.cdc.gov/drugresistance/about.html.
[1822] https://directorsblog.nih.gov/2018/02/20/powerful-antibiotics-found-in-dirt/#more-9758.
[1823] Hover BM, et al. *Nat Microbiol* 2018;3(4):415-22. PMID: 29434326.
[1824] Hover BM, et al. *Nat Microbiol* 2018;3(4):415-22. PMID: 29434326.

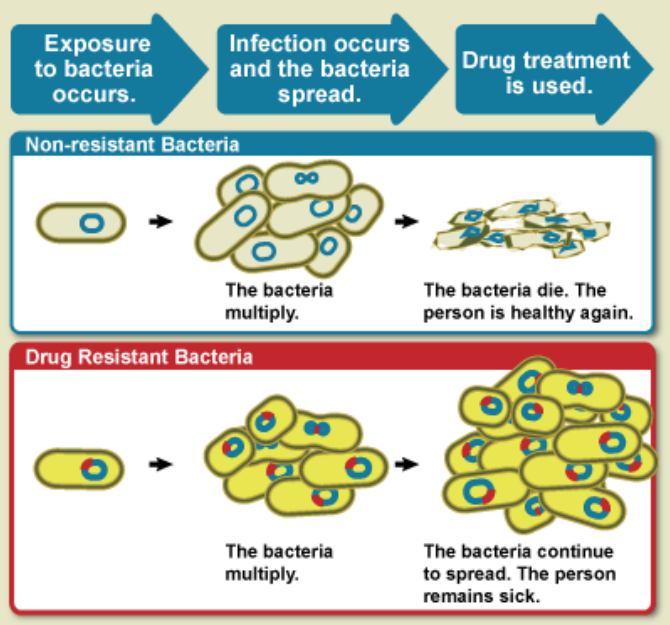

Figure 101. Diagram showing the difference between nonresistant bacteria and drug-resistant bacteria. Nonresistant bacteria multiply, and upon drug treatment, the bacteria die. Drug-resistant bacteria multiply, as well, but upon drug treatment, the bacteria continue to spread. Credit: NIAID.

MRSA bacteria commonly cause skin infections that can lead to life-threatening infections in other parts of the body.[1825] Another NIAID-supported study found that two common, inexpensive antimicrobials, clindamycin and trimethoprim-sulfamethoxazole, can help patients heal from MRSA skin abscesses.[1826] The 2017 reported findings suggest that current treatment options for MRSA still have a role, even as scientists continue to search for new antimicrobial products.[1827]

Fostering innovation in antibiotic development requires participation from both the private and public sectors. To meet this goal, NIAID, BARDA, and the Wellcome Trust are collaborating on a global public-private initiative called Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). Launched in 2016, this program is investing in early discovery and development of novel antibiotics, vaccines, and rapid diagnostics.[1828] As a partner in the public–private CARB-X program, NIAID has provided technical support and preclinical services to more than half of the CARB-X awardees to further advance the development of diagnostics, treatments, and vaccines.[1829]

[1825] https://www.niaid.nih.gov/research/antimicrobial-resistance.
[1826] Daum RS, et al. *N Engl J Med* 2017;376(26):2545-55. PMID: 28657870.
[1827] https://www.niaid.nih.gov/news-events/common-antimicrobials-help-patients-recover-mrsa-abscesses.
[1828] https://carb-x.org/about/overview/.
[1829] https://www.niaid.nih.gov/research/carb-x.

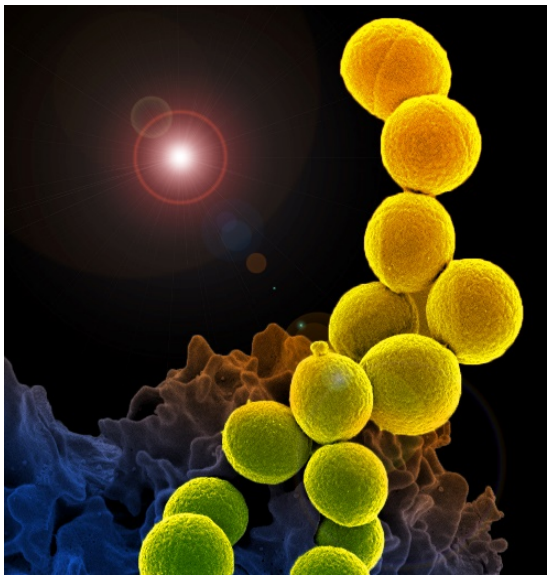

Figure 102. Colorized scanning electron micrograph of a white blood cell interacting with Methicillin-Resistant *Staphylococcus aureus* (MRSA), an antibiotic-resistant strain of *Staphylococcus aureus* bacteria. Credit: NIAID

NIAID and BARDA also launched the Antimicrobial Resistance Diagnostic Challenge in 2016, a $20 million federal prize competition seeking innovative, rapid point-of-care laboratory diagnostic tests to combat the development and spread of drug-resistant bacteria.[1830] The Challenge calls for new, innovative, and novel laboratory diagnostic tests that identify and characterize antibiotic-resistant bacteria or distinguish between viral and bacterial infections to reduce unnecessary uses of antibiotics, a major cause of antibiotic resistance.[1831] From 10 semifinalists designated in the first phase of the competition, 5 finalists were selected in 2018 to receive $100,000 each for the further development of prototype diagnostics.[1832]

NIH continues to explore other mechanisms that could lead to new treatments against infectious diseases. For example, NCATS researchers, in collaboration with a team of U.S. and international scientists, tapped into peptide libraries and succeeded where small-molecule screening failed. They have identified the first inhibitor of an enzyme long thought to be a potential drug target for fighting disease-causing parasites and bacteria.[1833] The target enzyme, cofactor-independent phosphoglycerate mutase (iPGM), is found in both parasites and bacteria. Several types of parasitic roundworms have iPGM, including *Brugia malayi* and *Onchocerca volvulus*, which infect roughly 150 million people living mostly in tropical regions. These parasites can cause devastating infectious diseases, such as river blindness. The enzyme is also found in bacteria, including *Staphylococcus aureus*, which can cause the hospital-borne infection MRSA, and

[1830] https://dpcpsi.nih.gov/AMRChallenge.
[1831] https://dpcpsi.nih.gov/AMRChallenge.
[1832] https://dpcpsi.nih.gov/AMRChallenge/FinalistsAnnouncement.
[1833] https://www.nih.gov/news-events/news-releases/international-scientific-teams-find-potential-approach-against-parasites.

Bacillus anthracis, which causes anthrax.[1834] With the discovery of this mechanism, treatments for certain parasitic or bacterial infections may be within reach.

Other Emerging Infectious Diseases

In addition to supporting research on influenza, Ebola, Zika, and AMR, NIH also funds research on other emerging infectious diseases and infectious agents, such as dengue and prions.

Worldwide, about 50 million cases of dengue infection occur each year, with 22,000 deaths, mostly in children.[1835] A human challenge trial was conducted in which volunteers were infected with dengue virus six months after receiving either an experimental dengue vaccine developed by NIAID scientists or a placebo injection. All 21 volunteers who received the vaccine were protected from infection, whereas all 20 placebo recipients developed infection.[1836] The results demonstrate that a human challenge trial could be a useful model to selecting candidate dengue vaccines for further evaluation to accelerate dengue vaccine development.[1837]

Figure 103. An Aedes mosquito biting. This species can transmit such diseases as chikungunya, dengue, and Zika. Credit: NIAID.

Creutzfeldt-Jakob disease (CJD) is an incurable and ultimately fatal transmissible, neurodegenerative disorder in the family of prion diseases.[1838] Sporadic CJD is the most common human prion disease, affecting about one in 1 million people annually worldwide, and although it was known to be transmissible by invasive medical procedures, transmission via skin had not been a common concern.[1839] In 2017, NIAID

[1834] https://www.nih.gov/news-events/news-releases/international-scientific-teams-find-potential-approach-against-parasites.
[1835] https://www.niaid.nih.gov/diseases-conditions/dengue-fever.
[1836] https://www.nih.gov/news-events/news-releases/experimental-dengue-vaccine-protects-all-recipients-virus-challenge-study.
[1837] Kirkpatrick B, et al. *Science Translational Medicine* 2016;8(330):330ra36. PMID: 27089205
[1838] https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Creutzfeldt-Jakob-Disease-Fact-Sheet.
[1839] https://www.nih.gov/news-events/news-releases/nih-scientists-collaborators-find-prion-protein-skin-cjd-patients.

scientists and collaborators at Case Western Reserve University School of Medicine reported the detection of an abnormal prion protein in the skin of nearly two dozen people who died from CJD. [1840] The study results raise questions about the possible transmissibility of prion diseases via medical procedures involving skin and whether skin samples might be used to detect prion disease. [1841]

Infectious Disease and Biodefense Infrastructure

NIH has developed and supported a broad infrastructure with the ability to support all levels of infectious disease and biodefense research. This vital support has been instrumental in developing the needed capabilities to prepare for, and respond to, infectious diseases and bioterrorism. Below are just some examples of NIH-supported projects aimed at developing, increasing, and maintaining that infrastructure.

NIAID leverages its versatile domestic and international infrastructure to respond rapidly to today's infectious disease emergencies and prepare for the next infectious threat, whether natural or manmade. Through a coordinated biodefense research effort with partners in industry, academia, and the federal Public Health Emergency Medical Countermeasures Enterprise, NIAID ensures that promising countermeasures for biological, chemical, and radiological public health threats can proceed to advanced development. NIAID, DoD, CDC, and BARDA supported the development of TPOXX, which was approved by the FDA in 2018 for the treatment of smallpox—the first drug with that indication.[1842] Two million courses of TPOXX were purchased by BARDA for the Strategic National Stockpile under Project BioShield for use in the event of a smallpox outbreak.[1843]

FIC published a FOA in August 2016 inviting applications from U.S. or African research institutions to plan research training and capacity building programs focused on emerging viral epidemics in collaboration with institutions in Guinea, Liberia, and Sierra Leone.[1844] Potential supported projects focused on a collaborative planning process to develop training approaches that will create sustainable research capacity for the early identification, transmission prediction, testing of public health responses, and assessing and addressing long-term health sequelae related to emerging viral diseases that have the potential for regional and global pandemics.[1845] In 2018, FIC announced another FOA aimed at strengthening the educational, clinical, and research capacity of health professions education institutions in Malawi and Zambia. The Health Professional Education Partnership Initiative (HEPI) is focused on improving the quality, quantity, and retention of health professionals to help these countries address their HIV epidemics and associated comorbidities and to improve the health of their populations.[1846] HEPI builds

[1840] Orrú C, et al. *Science Translational Medicine* 2017;9(417):eaam7785. PMID: 29167394
[1841] https://www.nih.gov/news-events/news-releases/nih-scientists-collaborators-find-prion-protein-skin-cjd-patients.
[1842] https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-indication-treatment-smallpox.
[1843] https://www.niaid.nih.gov/news-events/new-smallpox-drug.
[1844] https://grants.nih.gov/grants/guide/pa-files/PAR-16-407.html.
[1845] https://grants.nih.gov/grants/guide/pa-files/PAR-16-407.html.
[1846] https://grants.nih.gov/grants/guide/rfa-files/RFA-TW-18-002.html#_Part_2._Full.

on the achievements and lessons learned from previous efforts to further enhance educational and research programs, as well as partnerships and networks.

Standard methods for identifying bacterial infections often require isolating live bacteria from blood, urine, or spinal fluid and growing the bacteria in a laboratory culture, which can take several days. With advances in genetic sequencing technology, researchers have explored alternative approaches to diagnosing infections, such as assessing the body's immune response.[1847] When the immune system wards off an infection, immune cells activate certain genes, depending on whether the infection results from bacteria or viruses. Collectively, these distinct genes form what is called a "biosignature." Researchers supported by NICHD have now shown that it is possible to diagnose a bacterial infection from a small sample of blood—based on the immune system's response to the bacteria—in infants who are 2 months of age or younger with fevers.[1848] These preliminary findings indicate that biosignatures could ultimately lead to a fast and less-invasive test for diagnosing bacterial infections in infants with fevers.[1849]

Launched in 2016 by NIEHS in collaboration with CDC and other federal agencies, the 3-year, $9 million Ebola Biosafety and Infectious Disease Response Training Program will help approximately 35,000 first responders and workers—whose jobs may expose them to infectious diseases—protect themselves while also minimizing the spread of disease to others.[1850] The environmental infection control practices and hazard recognition skills taught will be applicable to any high-risk infectious disease that can be easily transmitted person to person and may result in high mortality rates.[1851] The training not only ensures the safety of those who respond to infectious disease outbreaks but also is essential for preventing further transmission.

With support from the U.S. Department of State's Office of the U.S. Global AIDS Coordinator and Health Diplomacy, FIC launched an R25 program in 2018 focused on educational activities that complement and enhance the training of a workforce to meet Africa's biomedical, behavioral, and clinical research needs.[1852] The program supports the establishment of an African Association for Health Professions Education and Research to serve as an interprofessional leadership and convening organization to network institutions across Africa. The objective is to jointly develop, disseminate, and share best practices, innovations, curricula, and policy, as well as engage in activities that will increase the quantity, quality, and retention of African health professionals to address the crisis in HIV/AIDS and its comorbidities on the continent.[1853]

[1847] https://www.nichd.nih.gov/newsroom/releases/newborninfections_082216.
[1848] Mahajan P, et al. *JAMA* 2016;316(8):846-57. PMID: 27552618.
[1849] https://www.nichd.nih.gov/newsroom/releases/newborninfections_082216.
[1850] https://www.niehs.nih.gov/news/newsroom/releases/2016/june1/index.cfm.
[1851] https://www.niehs.nih.gov/news/newsroom/releases/2016/june1/index.cfm.
[1852] https://grants.nih.gov/grants/guide/rfa-files/RFA-TW-18-001.html.
[1853] https://grants.nih.gov/grants/guide/rfa-files/RFA-TW-18-001.html.

Public Health Emergency Preparedness

Public health emergencies arise when unexpected incidents, both natural and man-made, have the potential to greatly influence the health of citizens, necessitating a rapid and robust response. HHS is a national leader in responding to such incidents, and many agencies within HHS have a critical role in ensuring an appropriate response to public health emergencies.

Summary of NIH Activities

NIH's commitment to disaster resilience has been the foundation for more than three decades of research. Multiple NIH Institutes, Centers, and grantees conduct research focusing on disaster preparedness, response, and recovery issues. These efforts have contributed to a deeper understanding of disaster risks and recovery and act to provide critical information when disasters strike. NIH supports research to address public health issues arising from natural and man-made disasters; biological, chemical, and radiological threats; and epidemics. NIH supports programs to help respond to public health emergencies in general, as well as to specific types of incidents, and several of the current efforts are highlighted below.

Emergency Preparedness Across NIH

To facilitate active, real-time surveillance of pathogens and foodborne disease, NLM's National Center for Biotechnology Information (NLM/NCBI) coordinates the Pathogen Detection Project, a multiagency collaboration that combines data from pathogen outbreaks with other information to identify closely related sequences.[1854] The system integrates bacterial pathogen genomic sequences originating in food, environmental sources, and patients to uncover potential food contamination sources, helping public health scientists investigate foodborne disease outbreaks.[1855] By the end of 2018, the system had integrated more than 300,000 pathogen genomes, which had been assembled using a new de novo assembler. Furthermore, AMR genes were identified in more than 200,000 pathogen genomes using the AMRFinder tool, which incorporates more than 4,500 reference proteins of acquired resistance.[1856] Additional NIH efforts to understand and respond to infectious diseases are highlighted in the Infectious Diseases and Biodefense section of Chapter 3.

[1854] https://www.ncbi.nlm.nih.gov/pathogens/.
[1855] https://www.ncbi.nlm.nih.gov/pathogens/about/.
[1856] https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/AMRFinder/.

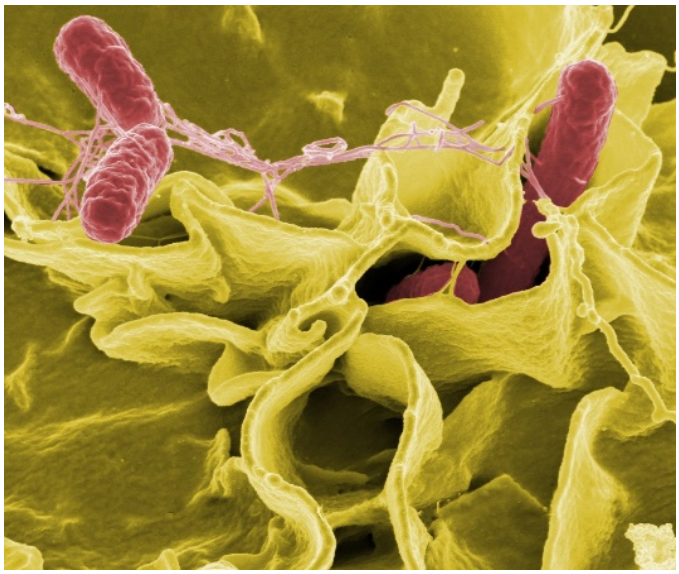

Figure 104. Salmonella bacteria, a common cause of food poisoning, invade an immune cell. Credit: NIAID.

In response to recent disasters and the research conducted in their wake, NIH has committed to fund the NIH Disaster Research Response (DR2) program.[1857] This program, developed by NIEHS in collaboration with NLM, aims to create a disaster research system consisting of coordinated environmental health disaster research data collection tools and a network of trained research responders. In July 2016, NIEHS and NLM published an article in the *International Journal of Environmental Research and Public Health* detailing the need for, and challenges associated with, conducting disaster research. The article highlights how the DR2 program, through the development of tools and training exercises, can help overcome some of those challenges.[1858]

The DR2 program encourages development of a network of trained, deployable research responders.[1859] Like all responders, researchers need training to be effective in their disaster roles. To support disaster science investigators, the DR2 website offers data collection tools, research protocols, and disaster research news and events, as well as a variety of training resources for preparing scientists to conduct research in the post-disaster field environment.

A key component of the DR2 program is the execution of major tabletop exercises to train environmental health researchers on incorporating data collection and research into disaster response and recovery.[1860] The workshops bring together federal, state, and local stakeholders from the academic, government, industry, and emergency response sectors to discuss conducting disaster research during a response. The workshops provide a forum for stakeholders to build relationships, share knowledge and resources, and identify opportunities for integrating research into the response. In July 2016, DR2 conducted a tabletop

[1857] https://dr2.nlm.nih.gov/about.
[1858] Miller A, et al. *Int J Environ Res Public Health* 2016;13(7):676. PMID: 27384574.
[1859] https://dr2.nlm.nih.gov/training-exercises#training.
[1860] https://disasterinfo.nlm.nih.gov/content/files/NIH_DR2_Workshop_Report_508.pdf.

exercise in Boston, Massachusetts. Approximately 160 participants discussed stakeholder engagement, concept of operations, data collection, challenges, and lessons learned from previous disasters.[1861]

Figure 105. An environmental enforcement boat passes in front of chemical tanks along the Elk River in West Virginia. Credit: Foo Conner/Flickr CC BY 2.0.

In addition to developing programs to aid during public health crises in general, NIH supports projects to reduce environmental exposures. NIEHS published a FOA in 2016 requesting applications for NIH-supported environmental health research in which an unpredictable event provides a limited window of opportunity to collect human biological samples or environmental exposure data.[1862] The primary motivation of the FOA is to understand the consequences of natural and man-made disasters or emerging environmental public health threats in the U.S. and abroad. The supported projects may lead to a better understanding of exposure–health outcome relations and provide data that will help inform public health emergency actions.

Two applications, aimed at identifying and reducing chemical exposures following a public health disaster, were awarded funding through the FOA. Oregon State University grantees have developed silicone wristbands to identify chemical exposures residents encountered after Hurricane Harvey.[1863] The wristbands are a simple, quick, and effective way to detect more than 1,500 different chemicals. The individualized information provided by the wristbands could inform ways to mitigate exposures and develop and implement interventions. University of Miami grantees are examining the impact of Hurricane Maria on PCB redistribution in and around Guánica Bay, Puerto Rico.[1864] They are also assessing changes in community exposure to PCBs through inhalation and consumption of contaminated seafood and fish. Results from the project will be utilized to develop strategies for reducing community exposure to PCBs.

[1861] https://disasterinfo.nlm.nih.gov/content/files/NIH_DR2_Workshop_Report_508.pdf.
[1862] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-16-005.html.
[1863] https://projectreporter.nih.gov/project_info_details.cfm?aid=9574673&icde=43198247.
[1864] https://projectreporter.nih.gov/project_info_description.cfm?aid=9607308&icde=43198226.

Rare and Undiagnosed Diseases

A rare disease is defined as one that affects fewer than 200,000 people and may involve chronic illness, disability, and premature death.[1865] Today, more than 7,000 rare disorders affect 25–30 million Americans.[1866] Thus, although the individual diseases may be rare, the total number of people with a rare disease is large. Rare diseases are often devastating and costly for patients, their families, and the nation, largely due to the severity of these conditions and because the diagnosis occurs long after the symptoms have appeared. Moreover, treatment is often unavailable, even after a disease is diagnosed, because it would require developing treatments for small, geographically dispersed populations.[1867]

Figure 106. Poster presenters at Rare Disease Day at NIH 2018. Daniel Soñé Photography, LLC.

Each year, NCATS and the NIH Clinical Center sponsor Rare Disease Day at NIH to raise awareness about rare diseases. Rare Disease Day takes place typically on or near the last day of February each year and strives to raise awareness among policymakers and the public about rare diseases and their impact on patients' lives.[1868] The hope is that these collaborative approaches have the potential to speed development of treatments for multiple rare diseases and ultimately help more patients more quickly.

[1865] https://www.ncbi.nlm.nih.gov/medgen/146261#Definition.
[1866] https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.
[1867] https://report.nih.gov/biennialreport10-11/chapter4/NIH_RDCRN.html.
[1868] https://ncats.nih.gov/rdd.

Figure 107. Panel discussion at NIH Rare Disease Day. Credit: Daniel Soñé Photography, LLC.

Summary of NIH Activities

NIH funding for rare diseases was $4,342 million in 2016, $4,613 million in 2017, and $5,227 million in 2018. Because rare and undiagnosed diseases can affect any organ system, funded research and activities are conducted throughout NIH, and several of NIH's activities in this area are presented here.[1869] Additional work relating to rare and undiagnosed diseases, as they pertain to specific health areas, is described in other sections of this chapter as appropriate.

Undiagnosed Diseases

Finding an underlying diagnosis for many conditions can be a long and frustrating experience.[1870] Individuals with rare conditions can go for extended periods without a diagnosis. These types of rare disorders are referred to as undiagnosed diseases.[1871] These diseases are difficult for doctors to diagnose because they are rare, have not previously been described, or are unrecognized forms of more common diseases. Toward that end, multiple efforts at NIH aim to provide answers to patients with mysterious conditions that have long eluded diagnosis and to advance medical knowledge about both rare and common diseases.

Through its programs and initiatives, NCATS focuses on rare diseases' commonalities and shared underlying molecular causes. By identifying commonalities across rare diseases, scientists have the potential to accelerate the development and demonstration of treatments for multiple diseases at once. NCATS supports the Rare Diseases Clinical Research Network (RDCRN), which consists of 21 consortia, studying more than 190 diseases at 454 clinical centers in 21 countries and is designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study

[1869] https://report.nih.gov/categorical_spending.aspx.
[1870] https://rarediseases.info.nih.gov/guides/pages/24/tips-for-the-undiagnosed.
[1871] https://www.nih.gov/news-events/undiagnosed-diseases-network-launches-online-application-portal.

enrollment, and data sharing.[1872] Through the RDCRN consortia, physician-scientists and their multidisciplinary teams work together with patient advocacy groups to study more than 200 rare diseases at sites across the nation.[1873]

Members of the NIH Common Fund's Undiagnosed Diseases Network (UDN)[1874] published a summary of the network's progress during the first 20 months of accepting applicants.[1875] During that time, the network accepted 601 participants who were undiagnosed by traditional medical practices, often after long and painstaking medical odysseys. Of those who competed their UDN evaluation in the first 20 months, 35 percent were given a diagnosis. Many of these diagnoses were rare genetic diseases, including 31 previously unknown syndromes.

Mendelian diseases are inherited diseases caused by dysfunction in a single gene. Researchers participating in NHGRI's Electronic Medical Records and Genomics (eMERGE) Network have found a new way to combine electronic health record information and genomics to discover new associations between genomic variants and Mendelian diseases.[1876] They looked at the data of more than 20,000 research participants and uncovered 18 novel gene-disease associations.

Rare Diseases

Researchers studying rare diseases face unique challenges—from tackling the large number of rare disorders and the complexity of each disease to the small patient populations and limited availability of data to the complications of optimizing study design, patient recruitment, and patient retention. For these reasons, NIH promotes multiple efforts to help the biomedical research community advance our understanding of the underlying disease mechanisms of rare diseases and develop potential therapeutics. Several of these advances are discussed below.

IRP researchers at NEI identified the causative gene mutation in patients with a rare, newly identified disease known as COMMAD (which stands for coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness). COMMAD patients are born only to deaf parents who have Waardenburg syndrome 2A, which is caused by mutations in the microphthalmia-associated transcription factor (*MITF*) gene. Patients with Waardenburg syndrome 2A, itself a rare disease, carry a single mutated copy of the *MITF* gene; if a child born to Waardenburg syndrome 2A patients carries two mutated copies of the *MITF* gene, that child will have COMMAD syndrome.[1877] The causative mutations were identified in two unrelated children born with the disease.

Smith-Lemli-Opitz syndrome (SLOS) is a rare genetic disease that disrupts the nervous system and can lead to microcephaly and other brain defects. SLOS currently has no cure or approved treatment.

[1872] https://ncats.nih.gov/rdcrn.
[1873] https://ncats.nih.gov/pubs/features/rdcrn-pidtc.
[1874] https://commonfund.nih.gov/diseases.
[1875] Splinter K, et al. *N Engl J Med* 2018;379(22):2131-9. PMID: 30304647.
[1876] Bastarache L, et al. *Science* 2018;359(6381):1233-9. PMID: 29590070.
[1877] George A, et al. *Am J Hum Genet* 2016;99(6):1388-94. PMID: 27889061.

Intramural scientists at NICHD discovered that SLOS appears to result from a buildup of a compound called 7-dehydrocholesterol (7DHC), a key step in how the body produces cholesterol.[1878] The researchers found that 7DHC caused a loss of a key signaling protein called β-catenin, which normally regulates how neurons develop. The researchers were able to use a drug to stabilize β-catenin, showing that this drug may be a potential treatment for SLOS. Knowing the specific process that leads to a symptom allows researchers to identify potential targets that may ultimately lead to new treatments.

The diversity of the immune system is generated by a process called V(D)J recombination, in which segments of DNA are cut and rejoined to produce a variety of new combinations—a process that is essential for maturation of the immune system. The proteins RAG1 and RAG2 function as the cleavers of DNA during V(D)J recombination and have been shown to be critical to the function of the immune system, as demonstrated by the more than 60 mutations in the genes encoding RAG1 and RAG2 that lead to severe combined immunodeficiency in humans or a milder form of immunodeficiency called Omenn syndrome. NIDDK intramural researchers showed that RAG1 and RAG2 proteins undergo significant movements in 3-D space during the process, cleaving the DNA in a nutcracker-like motion.[1879]

Fibrodysplasia ossificans progressiva (FOP) is a rare, so-far untreatable, debilitating genetic disorder that leads to episodic and recurrent heterotopic ossification (HO), in which extra bone develops in areas outside of the skeleton in soft tissues, such as skeletal muscle, tendons, and ligaments. This causes progressive locking of the joints, loss of mobility, and eventually premature death. Recent studies supported by NIAMS investigated two aspects of HO formation in FOP[1880] and found that agents targeting two different processes may be used to halt HO formation and decrease disease severity: the cellular response to low oxygen levels (hypoxia) brought about by inflammation,[1881] and the obligatory process of cartilage formation during HO.[1882] These studies identified several drug candidates, including some suitable for repurposing, that can effectively inhibit HO formation and prevent joint immobilization in FOP. One of the drug candidates, palovarotene, is undergoing a Phase II clinical trial in FOP patients.

Relatedly, researchers discovered that the HO that characterizes FOP originates from a type of progenitor cells called fibro/adipogenic progenitors.[1883] Using a mouse model of FOP, the investigators showed that fibro/adipogenic progenitor cells bearing the FOP mutation are a major contributor to both injury-induced and spontaneous bone formation and cause excess bone to accumulate in essentially all major anatomical sites where lesions form in FOP patients. In addition, the investigators showed the protein activin A is involved in HO formation and an antibody directed against activin A can suppress this process. Identifying the cells and molecules responsible for excessive bone formation may facilitate development of therapeutic approaches for FOP patients.

[1878] Francis KR, et al. *Nat Med* 2016;22(4):388-96. PMID: 26998835.
[1879] Kim MS, et al. *Mol Cell* 2018;70(2):358-70.e4. PMID: 29628308.
[1880] https://www.niams.nih.gov/newsroom/spotlight-on-research/new-insights-about-excess-bone.
[1881] Wang H, et al. *J Bone Miner Res* 2016;31(9):1652-65. PMID: 27027798.
[1882] Chakkalakal SA, et al. *J Bone Miner Res* 2016;31(9):1666-75. PMID: 26896819.
[1883] Lees-Shepard JB, et al. *Nat Commun* 2018;9(1):471. PMID: 29396429.

In FY 2018, NIAMS-funded researchers presented strong preclinical evidence to support further investigations of palovarotene as the first potential therapeutic agent for multiple hereditary exostoses (MHE), a rare disease characterized by the formation of multiple bony spurs or lumps covered by cartilage caps (also known as exostoses or osteochondromas) along the long bones and ribs.[1884] However, the observed suppression of bone growth in young animals that received high or medium doses suggests that the timing and dosing of palovarotene treatment should be important considerations when designing clinical studies for patients who have MHE. A clinical trial in another patient population has shown palovarotene to be relatively well tolerated with mild side effects.

Timothy syndrome is a rare genetic disorder characterized by life-threatening problems with irregular heart rhythm, webbed fingers and toes, and dental and bone abnormalities. Using genetically engineered mouse models of Timothy syndrome, researchers have found a link between bone formation and a mutation in the calcium channel that causes Timothy syndrome.[1885] Increasing activity in this calcium channel increased bone formation in a mouse model of Timothy syndrome and prevented bone loss in a model of osteoporosis. Identifying how this calcium channel mutation relates to bone health provides insights on potential targets for treating bone loss.

Investigators at NIAID and international colleagues discovered a genetic cause and potential treatment for a rare immune disorder called CHAPLE disease, or CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy.[1886] The condition can cause immunodeficiency, severe gastrointestinal distress, and deep vein blood clots. It is a form of Waldmann's disease, which was first described in 1961 by NIH scientist Thomas A. Waldmann, M.D.[1887] In the new study, NIAID researchers identified eculizumab, a therapeutic antibody approved to treat another rare condition, as a potential treatment for CHAPLE disease.[1888] NIAID physicians and others now are studying eculizumab in people with CHAPLE disease.

[1884] Inubushi T, et al. *J Bone Miner Res* 2018;33(4):658-66. PMID: 29120519.
[1885] Cao C, et al. *JCI Insight* 2017;2(22):95512. PMID: 29202453.
[1886] https://www.niaid.nih.gov/news-events/niaid-scientists-identify-cause-possible-treatment-life-threatening-gut-condition.
[1887] https://irp.nih.gov/catalyst/v26i5/thomas-a-waldmann-md.
[1888] Ozen A, et al. *N Engl J Med* 2017;377(1):52-61. PMID: 28657829.

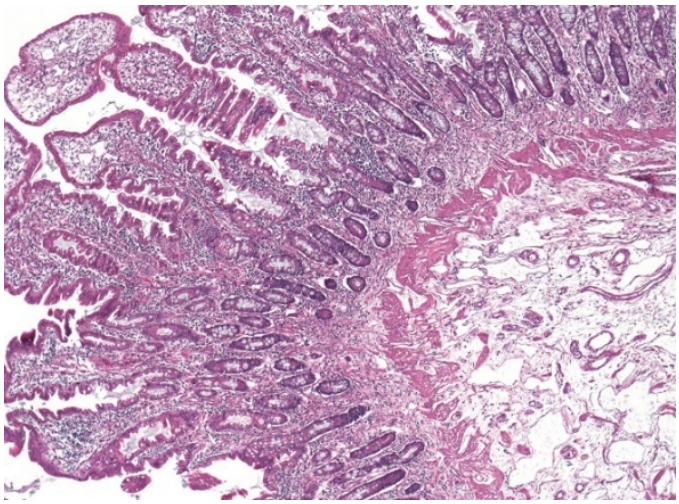

Figure 108. Light microscope image showing the gut tissue of a child with CHAPLE disease. The large white areas in the bottom right corner are enlarged lymphatic vessels, which can contribute to intestinal distress. Credit: NIAID.

Arterial calcification due to deficiency of CD73 (ACDC) is an adult-onset vascular disorder caused by mutations affecting the CD73 enzyme, which is involved in phosphate metabolism. The disorder leads to painful calcium buildup in the extremities, but the reason for these calcifications has been a mystery. By studying a mouse model of ACDC, researchers funded by NHLBI found that loss of CD73 causes a compensatory increase in inorganic phosphate production, which, in turn, increases free calcium in the blood.[1889] A related NHLBI-funded clinical trial is investigating whether patients with ACDC benefit from etidronate, a drug used to treat high blood calcium levels.[1890]

Researchers in an NHLBI-funded study used patient-derived cells to screen for potential drugs to treat a rare blood disorder, Diamond-Blackfan anemia (DBA), which affects the ability of bone marrow to produce red blood cells. By testing more than 1,200 small molecules on iPSCs from people with DBA, the researchers found one molecule that enhanced the production of red blood cells. The study demonstrates the utility of iPSC-based screens for drug discovery for DBA and other rare blood disorders.[1891]

Autoimmune pulmonary alveolar proteinosis (PAP) is a rare, chronic, and lethal lung disease in which proteins and lipids accumulate in the lungs, leading to respiratory failure. NHLBI-funded researchers found that when two patients with PAP were given statins for elevated cholesterol, the treatment also improved their breathing capacity. Next, they tested statins in a mouse model of PAP and found that statins improved the clearance of cholesterol from the lungs. These findings—grounded in an emerging understanding of disease mechanisms—point to statins as a potential treatment for PAP.[1892]

Intramural researchers at NIDCR collaborated with NIDCR-funded researchers to successfully treat a patient with leukocyte adhesion deficiency type 1 (LAD1), a rare immunodeficiency disorder that causes

[1889] Jin H, et al. *Sci Signal* 2016;9(458):ra121. PMID: 27965423.
[1890] https://www.clinicaltrials.gov/ct2/show/NCT01585402.
[1891] Doulatov S, et al. *Sci Transl Med* 2017;9(376):eaah5645. PMID: 28179501.
[1892] McCarthy C, et al. *Nat Commun* 2018;9(1):3127. PMID: 30087322.

recurring bacterial infections and severe periodontal disease that often leads to tooth loss at a young age. Previously, investigators demonstrated that an abnormally high level of a pro-inflammatory signaling molecule called IL-17 in LAD1 patients is a major cause of damaging inflammation around the teeth. In a pilot clinical study, researchers tested the use of ustekinumab, a drug approved by the FDA for psoriasis that blocks IL-17 production and found that 1 year of treatment with ustekinumab cured a non-healing skin wound and decreased oral inflammation in one LAD1 patient.[1893,1894]

Localized aggressive periodontitis (LAP) is a rare and severe form of periodontal disease that is more common in African American children and adolescents. NIDCR-funded scientists studying LAP epigenetics (the reversible, chemical modifications to DNA that turn genes on or off) found that people with LAP had epigenetic changes near genes that are part of the Toll-like receptor pathway, which plays a key role in immune responses.[1895] Further studies of these epigenetic changes may reveal how LAP progresses so quickly and why certain people are more likely to have the disease.

Lymphangioleiomyomatosis (LAM) is a rare, often fatal disease that affects women almost exclusively and is characterized by spreading of smooth muscle–like cells and cystic lesions in the lung. An available medication can stop the LAM cells from increasing rapidly, but it cannot make existing lesions shrink—it can only stabilize the disease. However, in other cancers, immunotherapies that involve the programmed cell death protein 1 (PD-1) receptor and its ligand, programmed death-ligand 1 (PD-L1), have shown promise in causing tumor regression and even curing some patients. NHLBI-funded research found increased levels of the ligand PD-L1 in the lungs of patients with LAM and in the lungs of a mouse model of LAM.[1896] Treating these mice with an anti-PD-1 antibody enhanced their survival, indicating this pathway as a potential therapeutic target for LAM.

Mutations in the ryanodine receptor calcium release channels can impact calcium (Ca^{2+}) movement in skeletal muscle cells, leading to the potentially fatal disease malignant hyperthermia. While drugs are in development that can prevent disease-causing Ca^{2+} leakage, they are unlikely to be helpful in treating people who have the same symptoms because of an inability to transmit Ca^{2+}. In a truly textbook example of translational science, researchers developed a new mouse model of malignant hyperthermia that is not caused by Ca^{2+} leakage, determined the mechanism of the disease pathology, and effectively treated the animals with an FDA-approved drug.[1897]

X-linked hypophosphatemia (XLH) is a rare inherited form of rickets that leads to impaired bone growth and development in children and adolescents and problems with bone mineralization throughout a patient's life. In April 2018, FDA approved the monoclonal antibody Crysvita (burosumab-twza) for adults and children ages 1 and older who have XLH.[1898] The drug's development stems from an NIH grant funded

[1893] https://penntoday.upenn.edu/news/penn-dental-research-leads-to-treatment-for-rare-gum-disease.
[1894] Moutsopoulos NM, et al. *N Engl J Med* 2017;376(12):1141-6. PMID: 28328326.
[1895] Shaddox LM, et al. *Clin Epigenetics* 2017;9:94. PMID: 28883894.
[1896] Maisel K, et al. *Am J Respir Cell Mol Biol* 2018;59(6):723-32. PMID: 30095976.
[1897] Lee CS, et al. *Nat Commun* 2017;8:14659. PMID: 28337975.
[1898] https://www.fda.gov/news-events/press-announcements/fda-approves-first-therapy-rare-inherited-form-rickets-x-linked-hypophosphatemia.

in 1993 that led to the discovery of the causative genetic defect and from other NIH-supported advances into the disease's underlying mechanism.

Angelman syndrome (AS) is a genetic neurodevelopmental disorder that causes global developmental delay, intellectual disability, epilepsy, and other symptoms. It occurs in 1 in 12,000 to 20,000 people. Research in mouse models has indicated that levodopa, a drug used to treat Parkinson's disease, could target the underlying pathological process of AS, with potentially beneficial effects in children with AS. Because levodopa is being prescribed off label for children with AS by an increasing number of clinicians without science-based FDA approval for this use, researchers conducted a randomized, controlled clinical trial of levodopa to assess its effects in 4- to 12-year-old children with AS. At the dosage used in the year-long trial, no clinically or statistically significant improvements were observed in neurodevelopmental, cognitive, or behavioral outcomes in children treated with levodopa versus those receiving a placebo.[1899] This information is important for physicians and health care providers to make informed decisions regarding effective treatments for AS.

In a recent clinical trial, NICHD intramural researchers showed that a new approach to replacing the hormone cortisol is a safe and effective way to treat difficult-to-treat classic congenital adrenal hyperplasia.[1900] The new treatment involves a small medical pump that delivers round-the-clock infusion of this critical hormone for patients. The new approach is more effective, because the infusion mimics the natural circadian rhythm of cortisol secretion throughout the day, which peaks early in the morning and declines to the lowest level shortly after midnight before rising again.

Osteogenesis imperfecta (OI), or brittle bone disease, is a rare genetic disorder affecting the protein collagen, which is found in bone, teeth, skin, and tendons. People with the disorder have bones that can break easily, often from a mild impact or for no apparent cause. Previously, all the known forms of OI were found to arise from genes on the autosomal, or non-sex, chromosomes. NICHD intramural researchers, along with colleagues from Thailand and Switzerland, discovered the first form of OI resulting from a gene defect in *MBTPS2* on the X chromosome, which encodes a protein called site-2-protease (S2P).[1901] Mutant S2P undermines bone strength. Learning how this genetic defect results in impaired bone formation may lead to treatments for this rare, debilitating disease.

Investigators from the Brittle Bone Disorders Consortium, an RDCRN consortium collaboratively funded by several NIH ICs (including NIAMS), set out to systematically study the factors, including delivery methods, that affect the fracture rates in OI newborns. The researchers analyzed data from the OI Linked Clinical Research Centers (which have become part of the Brittle Bone Disorders Consortium) with self-reported outcomes from 540 OI patients. The results show that the subtype of OI, which correlates to OI severity, is the most important factor that determines a baby's risk of fracture during birth.[1902] Contrary

[1899] Tan WH, et al. *Am J Med Genet A* 2018;176(5):1099-1107. PMID: 28944563.
[1900] Nella AA, et al. *J Clin Endocrinol Metab* 2016;101(12):4690-8. PMID: 27680873.
[1901] Lindert U, et al. *Nat Commun* 2016;7:11920. PMID: 27380894.
[1902] Bellur S, et al. *Genet Med* 2016;18(6):570-6. PMID: 26426884.

to popular belief, the method of delivery does not affect newborn fracture risk within the same subtype of OI; cesarean delivery does not protect against fractures during birth of OI babies.

Employing Gene Therapy to Treat Rare Diseases

Gene therapy is a transformational technology that allows new genetic material to be introduced into patient cells to compensate for abnormal genes or to make a necessary protein. With great hope, excitement and caution, NIH has supported several efforts in which gene therapy has been used to introduce a normal copy of the gene to restore the function of the protein in several diseases, including rare diseases.

Pompe disease is a rare muscle disease caused by the deficiency of an enzyme called acid alpha-glucosidase (GAA), which leads to the buildup of a complex sugar called glycogen in the body's cells. The accumulation of glycogen in certain organs and tissues, especially muscles, impairs their ability to function normally. Since 2006, people in the U.S. with Pompe disease have been treated with infusions of GAA produced by specially engineered cells in laboratories. NIH funded a mouse study to determine if a single treatment with a modified virus that delivers the *GAA* gene to the liver can induce immune tolerance against the laboratory-generated GAA, but the results of this work also showed that the technique could potentially replace the existing GAA enzyme-replacement therapy.[1903] These results directly contributed to a clinical trial that NIAMS began funding in FY 2017. Additionally, this approach of targeting expression of therapeutic genes to the liver holds significant promise for other rare lysosomal storage disorders that have similar pathologies as Pompe disease, as well as for other diseases, such as hemophilia.

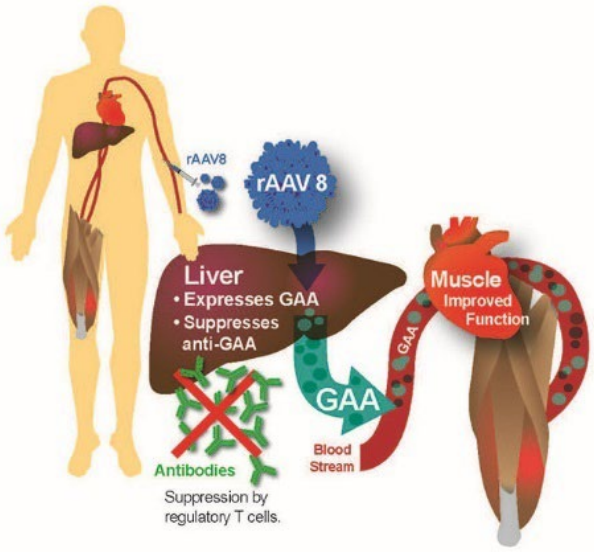

Figure 109. Illustration of the gene therapy approach for Pompe disease, Credit: NCATS.

[1903] Han SO, et al. *Mol Ther Methods Clin Dev.* 2017;4:126-36. PMID: 28344998.

Recessive dystrophic epidermolysis bullosa patients have painful blisters and chronic wounds of the skin and mucous membranes and are prone to infections, scarring, malnutrition, and aggressive skin cancer. Currently, the only treatment for recessive dystrophic epidermolysis bullosa skin lesions is palliative wound care. In ex vivo gene therapy, a patient's epidermal cells are grown in culture, and a virus is used to introduce a normal version of the type VII collagen gene. The corrected cells are then grown in flat sheets that can be lifted off the culture dish and grafted back onto the patient's wounds. Results from a Phase I clinical trial testing the approach in four patients demonstrated that grafts were well tolerated and no serious adverse events occurred.[1904,1905] In some cases, the grafts healed chronic wounds that had not healed spontaneously in the past 5 years. FDA has given approval for continued testing of this therapy in a Phase IIA clinical trial that will enroll adolescents age 13 or older.

Patients born with two mutated copies of the *RPE65* gene suffer from a debilitating congenital blinding disease called Leber congenital amaurosis. In 2017, FDA approved Luxturna (voretigene neparvovec-rzyl) as the first gene therapy for the treatment of an inherited retinal disease in patients.[1906] The approval of this gene therapy approach is the culmination of years of research funded by NEI and could pave the way for gene therapy as a treatment for many other inherited retinal diseases.

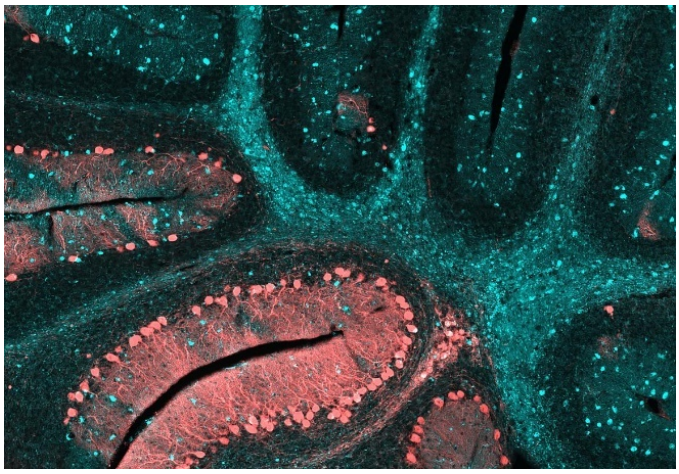

Figure 110. The cerebellum of a mouse brain affected by Niemann-Pick Type C. Credit: NICHD.

Many rare genetic diseases affect the nervous system, and the blood–brain barrier presents a significant obstacle for gene delivery. The discovery that a specific serotype of AAV-9 could cross the blood–brain barrier[1907] represented a major breakthrough in the field. For the first time, NIH researchers have demonstrated in mice that gene therapy may be the best method for correcting the single faulty gene

[1904] Siprashvili Z, et al. JAMA 2016;316(17):1808-17. PMID: 27802546.
[1905] https://www.niams.nih.gov/newsroom/spotlight-on-research/genetically-modified-skin-grafts-show-promise-treating-epidermolysis.
[1906] https://www.nei.nih.gov/about/news-and-events/news/nih-vision-researcher-t-michael-redmond-recognized-champalimaud-vision-award#:~:text=Vision%20researcher%2C%20T.-,Michael%20Redmond%2C%20Ph.,the%20back%20of%20the%20eye.
[1907] Foust KD, et al. *Nat Biotechnol* 2009;27:59–65. PMID 19098898.

that causes Niemann-Pick disease, type C1 (NPC1).[1908] Niemann-Pick disease is a rare and fatal disorder of the central nervous system that has no cure. The gene therapy involved inserting a functional copy of the *NPC1* gene into mice with the disease; the treated animals were then found to have less severe NPC1 symptoms.[1909]

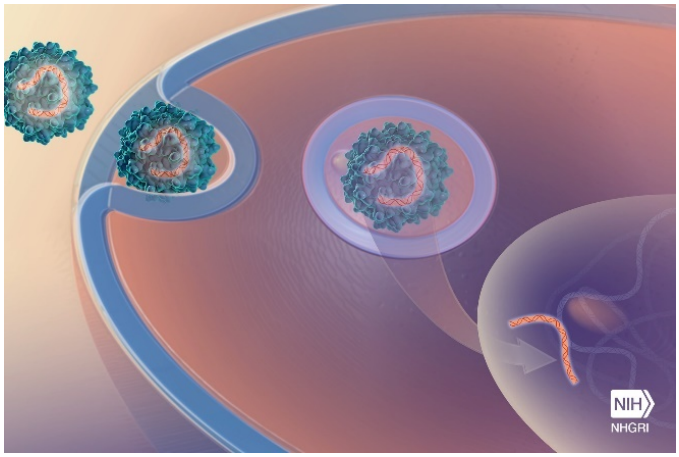

Figure 111. Illustration of gene therapy for Niemann-Pick disease being tested in mice. This involved inserting a functional copy of the *NPC1* gene into mice with the disease. Credit: NHGRI.

Microbiome

It has become increasingly clear that the healthy human body is teeming with microorganisms, many of which play essential roles in health and disease. The human microbiome, as this ecosystem of microbes that live within us has been named, consists of a large—but still undetermined—number of microbes. Although bacteria make up the majority of the microbes calling our bodies home—outnumbering our cells 10 to 1 in a healthy human adult—other residents include single-celled archaea and fungi. Several types of viruses also live in the nose and gut of otherwise perfectly healthy people.

Interactions between hosts and commensal, or beneficial, microbes have been demonstrated to play a key role in a range of important functions, including regulation of metabolic processes and immune function, as well as reproduction and wound healing. Conversely, evidence indicates that dysregulated ("dysbiotic") microbial communities can contribute to a wide range of diseases and conditions, including obesity, diabetes, cancer, and autoimmune diseases.

[1908] https://www.genome.gov/news/news-release/Gene-therapy-shows-promise-for-treating-Niemann-Pick-disease-type-C1.
[1909] Chandler RJ, et al. *Hum Mol Genet* 2017;26(1):52-64. PMID: 27798114.

Figure 112. Microbes inhabit just about every part of the human body, outnumbering human cells by 10 to 1. Credit: Darryl Leja, NHGRI.

Summary of NIH Activities

Many NIH ICOs fund research on the microbiome, including NCI, NIA, NIAID, NIAMS, NICCD, NICHD, NIDCR, NIEHS, NINR, OAR, and the NIH Common Fund. Studies range from those aiming to develop tools for studying the microbiome to those using available tools to understand how the microbiome affects health and disease.

Trans-NIH Activities

A key project demonstrating the NIH investment in this area is the Human Microbiome Project (HMP).[1910–1913] HMP was funded by the NIH Common Fund from 2007 to 2016 and developed research resources to enable the study of the microbial communities that live in and on our bodies and the roles they play in human health and disease. One example of such a resource includes data that have allowed researchers to answer numerous questions about the way the microbiome interacts with our bodies and how it affects our health. Since the inception of HMP, NIH investment in microbiome research at the NIH has increased more than fortyfold and spans more than 20 NIH ICs. Results of HMP are also described in the Digestive Diseases subsection of the Chronic Diseases and Organ Systems section in this chapter.

[1910] http://www.hmpdacc.org/overview/.
[1911] http://commonfund.nih.gov/hmp.
[1912] Lloyd-Price J, et al. *Nature* 2017;550(7674):61-6. PMID: 28953883.
[1913] Nash AK, et al. *Microbiome* 2017;5(1):153. PMID: 29178920.

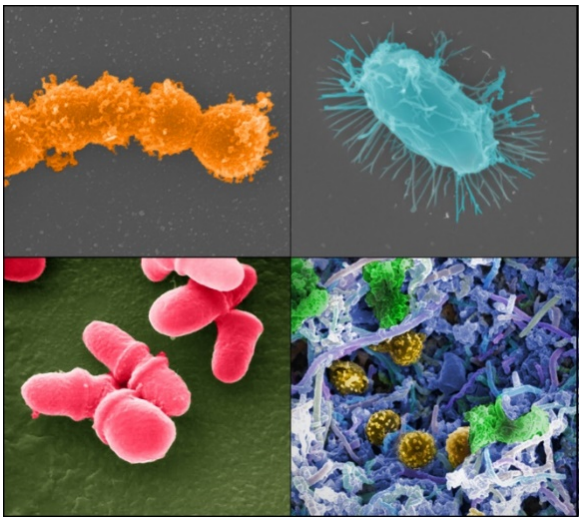

Figure 113. The Human Microbiome Project, which was launched by NIH in 2007, provided the first glimpse of the microbial diversity of healthy humans and is exploring the possible relationships between particular human diseases and the microbiome. (Clockwise from top left): *Streptococcus* (Credit: Tom Schmidt); microbial biofilm of mixed species, from human body (Credit: A. Earl, Broad Institute/MIT); *Bacillus* (Credit: Tom Schmidt); *Malassezia lopophilis* (Credit: J.H. Carr, CDC). Credit for composite image: Jonathan Bailey, NHGRI.

Understanding of the Microbiome

To better understand the microbiome and how it supports health in the human body, researchers need tools to study the bacteria that compose the microbiome. This poses unique challenges, because the commensal bacteria that grow in our bodies cannot be studied using the same methods that are used to study other bacteria, such as those that cause infections.

To address this difficulty, NIDCR-supported researchers are developing innovative strategies to grow oral bacteria that previously could not be cultured and studied in the laboratory.[1914] One group used specific growth supplements and a combination of oral bacteria commonly found in biofilms—slimy layers of bacteria that are attached together on a surface—to successfully grow five strains of beneficial oral bacteria, thus enabling researchers to study these strains more closely.[1915] These studies suggest that many oral bacteria are dependent on other bacteria for their survival, which may lead to the development of new techniques to culture more of the oral microbiota.

In 2018, 10 projects were funded by NCCIH seeking data about the variety of compounds that result from bacteria interacting with food in the human gut. The aim of these projects was to determine whether these compounds could be consistently measured and identified. Using these measurement tools, researchers could then more precisely study the processes underlying human health.[1916]

[1914] https://projectreporter.nih.gov/project_info_description.cfm?aid=9476781&icde=42205563.
[1915] Vartoukian SR, et al. *PLoS One*. 2016;11(1):e0146926. PMID: 26764907.
[1916] https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-18-003.html.

This expansion of microbiomics—the scientific study of the microbiome—complements the transdisciplinary studies being conducted in related fields, such as genomics, metabolomics, and proteomics. To advance the growing importance of -omics in nursing science, NINR has developed the Omics Nursing Science and Education Network website in collaboration with NCI and NHGRI. The goal is to advance -omics nursing research and education and to facilitate collaborations, mentoring, and access to training opportunities in the field.[1917]

Role of the Microbiome in Health

Researchers have found that different influences change the composition of bacteria in our bodies over the lifespan, with profound and surprising effects on our health. Many questions remain in our understanding of the mechanisms by which bacteria interact with our own body cells and how those interactions keep us healthy.

Research funded by NIEHS has shown that environmental exposures occurring during specific developmental windows are linked to persistent, functional changes in the microbiome, which may ultimately lead to disease later in life. To understand how this happens, NIEHS supports the initiative entitled The Role of the Microbiome in the Developmental Origins of Health and Disease.[1918] Projects funded under this initiative use various animal models to understand how changes to the microbiome occur due to a range of common environmental exposures and the ways in which they are linked to a diverse set of health outcomes. A broad range of exposures are considered—for example, air pollution and flame retardants. By relating exposures, changes in the microbiome, and health outcomes—which include metabolic and behavioral changes—this initiative will help develop a deeper understanding of the importance of the human microbiome on health throughout the lifespan.

In another study funded by NIEHS, alterations in the gut microbiome in children as young as six weeks old were shown to be linked to the levels of arsenic to which the infants were likely to have been exposed. These findings depended on sex and feeding method, with microbiome changes observed only in male infants that were fed formula. This finding underscores the complexity of interacting factors that influence how the microbiome responds to early life environmental exposures.[1919]

NIEHS has also supported research about the microbiome through various grants, programs, and workshops, including the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM^2) at Emory University School of Nursing. This program is the first of the NIEHS–U.S. Environmental Protection Agency (EPA) jointly funded Centers for Children's Health and Disease Prevention Research to study how the microbiome affects preterm birth and infant health. C-CHEM^2 aims

[1917] https://omicsnursingnetwork.net.
[1918] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-18-005.html.
[1919] Hoen AG, et al. *Sci Rep* 2018;8(1):12627. PMID: 30135504.

to examine the relationship between prenatal and postnatal environmental exposures, the infant microbiome, and infant neurodevelopment.[1920]

Differences in the microbiome have also been implicated in effects on metabolism. NIEHS-funded researchers found that exposure to traffic-related air pollution impacted the gut microbiome. Higher exposures to traffic-related air pollution was associated with lower levels of the beneficial bacteria associated with lower fasting glucose levels, as well as higher levels of the other bacteria associated with high fasting glucose levels. This suggests that one way in which air pollution may influence metabolic health is through the gut microbiota.[1921]

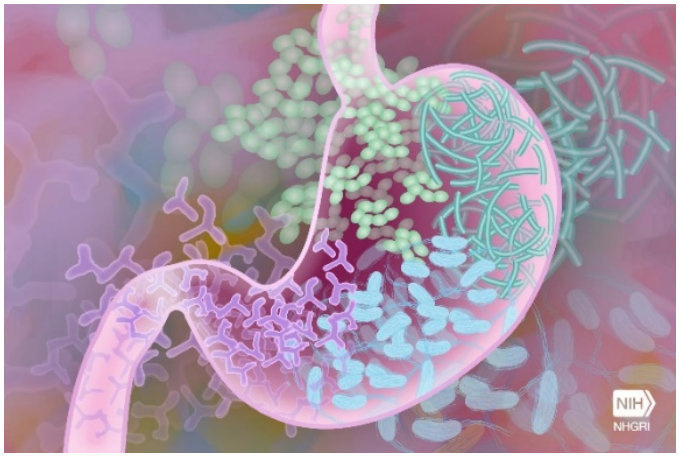

Figure 114. Bacterial strains in the guts of humans and chimpanzees diverged and began to evolve separately 5 million years ago and those in humans and gorillas, 15 million years ago. Humans and apes evolved into a new species at about the same time. A mutually beneficial relationship between gut bacteria and animal hosts may contribute to the formation of a new species. Credit: Darryl Leja, NHGRI.

Changes in metabolism contributing to insulin resistance also occur with age. To understand why older adults commonly display insulin resistance and increased blood sugar, NIA intramural investigators studied aged mice and macaques and found that aging is associated with changes in intestinal microbes. Beneficial bacteria called *Akkermansia muciniphila* decreased and pro-inflammatory microbes increased. The research team also showed that this inflammatory chain of events and subsequent insulin resistance in aging was reversible, as supplementation with either *A. muciniphila* or the antibiotic enrofloxacin increased the abundance of *A. muciniphila* and restored normal insulin response in aged mice and macaques. This finding indicates that the microbiome could potentially be targeted to reverse age-associated insulin resistance.[1922]

The gut microbiome, far from influencing only metabolism, is also studied in relation to reproduction and fertility. NICHD published a FOA in FY 2018 to support research to examine the role of the gut microbiome in regulating metabolism and reproduction, as well as its impact on fertility status. The overarching goal is to gain fundamental insight into this relationship and how it is modulated through signaling networks

[1920] http://www.nursing.emory.edu/c-chem2/index.html.
[1921] Alderete TL, et al. *Environ Res*. 2018;161:472-78. PMID: 29220800.
[1922] Bodogai M, et al. *Sci Transl Med*. 2018;10(467).eaat4271. PMID: 30429354.

in the brain. The results of the study could lead to the development of diagnostic markers or signature microbiomes for reproductive and metabolic failure.[1923]

Using mice that model the effects of menopause in women, NIAMS-supported researchers showed that a probiotic supplement containing a specific bacterium found in some yogurt and cheese products was able to protect against bone loss and reduce signs of inflammation. These results demonstrate the importance of gut microbiota in bone health in mice, suggesting that probiotics could be a potential therapeutic option for preventing postmenopausal bone loss.[1924]

One mechanism by which reproduction may be impacted by the microbiome is not simply in the presence or absence of commensal bacteria but in the diversity of such bacteria. PCOS is a disorder that affects 5–15 percent of women worldwide, often leading to higher androgen levels and infertility, as well as increased risk of miscarriage and pregnancy complications, obesity, type 2 diabetes, and CVD. Scientists compared microbiome samples from women with PCOS, women without PCOS, and women with polycystic ovaries but none of the other symptoms of PCOS. They found that the women with PCOS had the least diverse gut microbiomes of the three groups. Testosterone levels and overall androgen levels also correlated with microbial diversity: The higher a woman's levels of these hormones, the less diverse her gut microbiome was likely to be. [1925,1926]

Reproductive health has been found to be associated with differences in microbes at other sites within the human body, as well. In an observational study, the placental microbiome was different for women who had given birth preterm compared with full term, regardless of whether they had signs of infection. NICHD-supported researchers had analyzed the placental microbiome of women with chorioamnionitis (affecting the fluid-filled membrane that surrounds the fetus), funisitis (affecting the blood in the umbilical cord), or neither infection.[1927]

Healthy, diverse communities of bacteria in the intestinal tract of infants are known to confer life-long health benefits, including protection against risks of chronic diseases and other disorders as a child grows into adulthood. This includes diabetes, allergies, and inflammatory bowel disease.

To determine whether breastfeeding was a means by which maternal bacteria is transferred to offspring, NICHD-supported researchers studied healthy mother-infant pairs and analyzed microbes in samples of breast milk, swabs from the mother's skin surrounding the nipple, and infant stool. They found the same distinctive microbes in each sample, demonstrating that breast milk bacteria influence the establishment and development of beneficial bacteria in the infant gut, which could affect health throughout life.[1928]

Finally, research using mouse models has shown that beneficial bacteria on the skin work with the immune system to defend against disease-causing microbes and accelerate wound healing. Researchers funded by

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[1923] https://grants.nih.gov/grants/guide/pa-files/pa-18-838.html.
[1924] Li JY, et al. *J Clin Invest* 2016;126(6):2049-63. PMID: 27111232.
[1925] https://www.nichd.nih.gov/newsroom/news/020218-PCOS.
[1926] Torres PJ, et al. *J Clin Endocrinol Metab* 2018;103(4):1502-11. PMID: 29370410.
[1927] Puri K, et al. *PLoS One* 2016;11(9):e0162734. PMID: 27658190.
[1928] Pannaraj PS, et al. *JAMA Pediatr* 2017;171(7):647-54. PMID: 28492938.

NIAID observed the reaction of mouse immune cells to *Staphylococcus epidermidis*, a bacterium found on human skin that does not normally cause disease. They found that immune cells recognized *S. epidermidis* and produced molecules that encouraged production of unusual T cells with genes associated with tissue healing and antimicrobial defense. In contrast, immune cells recognized disease-causing bacteria by producing other molecules, which led to the production of T cells that stoke inflammation.[1929,1930] Eventually, clinicians may be able to accelerate wound healing and prevent dangerous infections by mimicking the processes initiated by the microbiome.

Taken together, this research provides a deeper understanding of how the human body relies on the microbes it hosts to maintain healthy function.

Role of the Microbiome in Disease

Research has also been performed to understand the role of the microbiome in specific diseases. Although allergy, asthma, and atopic dermatitis (or eczema—an inflammatory skin disease that can make skin dry and itchy, cause rashes, and lead to skin infections) have long been thought to be initiated in part by infections, direct evidence supporting this idea has been limited. NIH has funded research that has provided insight in this regard.

In 2016, NIAID-funded scientists identified several patterns of microbial communities in the stool of infants. Every pattern of organisms potentially results in a different metabolic environment in the gut based on what the organisms produce as they grow. One particular pattern of microbes in these infants appeared to influence immune cell populations and promote the development of allergy and asthma. Taking a step further, the scientists identified a relationship between a set of metabolites resulting from the growth of this particular pattern of organisms and increased risk for allergy.[1931,1932]

NIAID-led research conducted in mice indicates that a single gut infection can create long-lasting immunological damage. Scientists infected mice with *Yersinia pseudotuberculosis*, a foodborne bacterium that also infects people. Although some mice recovered normally, others exhibited long-term abnormalities in the gut, including enlarged lymph nodes and chronic inflammation. The abnormalities persisted despite clearance of *Y. pseudotuberculosis*, leading the researchers to suspect that the microbiota might play a role in maintaining the harmful immune changes triggered by the infection. Mice treated with antibiotics to clear the microbiota had reduced inflammation, suggesting that targeting defined beneficial microbes may be a strategy to restore immune balance.[1933,1934] Research on allergy and

[1929] https://www.niaid.nih.gov/news-events/nih-scientists-find-microbes-skin-mice-promote-tissue-healing-immunity.
[1930] Linehan JL, et al. *Cell* 2018;172(4):784-96.e18. PMID: 29358051.
[1931] https://www.niaid.nih.gov/news-events/infant-gut-microbiome-appears-shape-allergy-risk-altering-immune-responses.
[1932] Fujimura KE, et al. *Nat Med* 2016;22(10):1187-91. PMID: 27618652.
[1933] https://www.youtube.com/watch?v=Lcgzb3cfYVM.
[1934] Fonseca DM, et al. *Cell* 2015;163(2):354-66. PMID: 26451485.

asthma is also described in the Asthma and Allergy subsections of the Chronic Diseases and Organ Systems section in this chapter.

Inquiry related to other diseases—including work in diabetic foot ulcers (DFUs), cancer, liver disease, periodontal disease, and HIV—have also improved our understanding of the microbiome.

DFUs are common chronic wounds affecting 15–25 percent of diabetes patients, some of whom will, as a consequence, require amputation. Researchers conducted a longitudinal study of DFUs in a cohort of diabetes patients and identified characteristics of dynamic microbial populations for wounds that healed quickly and for wounds that persisted. The study yielded four different microbial community types with different percentages of microbial classes, such as predominantly *Staphylococcus* (predominantly *Staphylococcus aureus*) or highly diverse populations of more than 20 different microbes. The microbial populations of wounds that healed quickly were unstable—over time, they changed from one community type to another more frequently. In wounds that took longer to heal, fewer transitions from one community type to another occurred over the observation period. The researchers concluded that effective clinical control of chronic wounds disrupts bacterial colonization of the wound. These findings about microbiome dynamics may also be applicable to chronic wounds associated with a broad array of health conditions.[1935]

Periodontal disease is caused by an amplified inflammatory response to dental plaque. An NIDCR-funded GWAS analyzed microbial DNA from dental plaques from about 1,000 people with different levels of severity of periodontal disease. Researchers identified six different complex periodontal traits associated with unique disease profiles and specific types of bacterial communities. Fundamental studies like this suggest that periodontal disease may not be a single disorder but a group of harmful conditions, each with a distinct genetic, bacterial, and inflammatory signature.[1936]

Dental caries are the result of harmful oral biofilms that create a highly acidic microenvironment that erodes tooth enamel. NIDCR-supported scientists developed a method to map the 3-D architecture of the biofilm of the most common caries-causing oral pathogen, *Streptococcus mutans*, and can now pinpoint where damaging acids accumulate at the molecular level and how the bacteria and the matrix encourage biofilm growth. These findings suggest that targeting and altering biofilm microenvironments may be a new therapeutic approach for a variety of biofilm-associated diseases.[1937]

The presence of advanced fibrosis—or overgrowth and hardening of tissue—in NAFLD is the most important predictor of liver mortality. An NIEHS-funded study identified 37 bacterial species in the fecal microbiomes of study subjects, which were then used to construct a model able to distinguish mild or moderate NAFLD from advanced fibrosis with nearly 94 percent diagnostic accuracy.[1938]

[1935] Loesche M, et al. *J Invest Dermatol* 2017;137(1):237-44. PMID: 27566400.
[1936] Offenbacher S, et al. *Hum Mol Genet* 2016 May 15;25(10):2113-29. PMID: 26962152.
[1937] Hwang G, et al. *Sci Rep* 2016;6:32841. PMID: 27604325.
[1938] Loomba R, et al. *Cell Metab* 2017;25(5):1054-62.e5. PMID: 28467925.

In the context of HIV, the microbiome is thought to influence the effect of both prevention and treatment strategies. The 3rd International Workshop on Microbiome in HIV Pathogenesis, Prevention, and Treatment in 2017 was a two-day event that included invited lectures by key opinion leaders, oral abstract presentations and poster presentations, and discussion in workshop settings. The conference engaged basic scientists and clinicians from the HIV field and leading scientists involved in microbiome research, including bioinformatics experts. The aim of the workshop was to provide increased opportunities for discussion and exchange of knowledge following formal presentation of the latest research on HIV and the microbiome. OAR has been involved in the development and facilitation of this annual workshop since 2014, in partnership with NIAID and Virology Education.[1939]

Despite extensive research into the relationship between the gut microbiome and cancer, the role of gut bacteria in the formation of liver cancer has remained poorly understood. Researchers from the NCI IRP have found a connection between bacteria in the gut and antitumor immune responses in the liver. The study showed that bacteria found in the gut of mice affect the liver's antitumor immune function. The findings have implications for understanding the mechanisms that lead to liver cancer and for therapeutic approaches to treat them.[1940] Substantial research in cancer is also reported in the Cancer section in this chapter.

Development of Novel Therapies

Using the insights gained from tools developed to study the microbiome and a deeper understanding of the role of the microbiome in both health and disease, researchers have developed novel treatments to address unfavorable patterns in the microbiome.

Eczema is linked to an increased risk of developing asthma, hay fever, and food allergy. Earlier research by NIH and others showed that individuals with eczema have different skin bacteria than those who do not. Based on preclinical findings, NIAID investigators designed an early-stage clinical trial to test the safety and potential benefit of a treatment for people with eczema containing live *Roseomonas mucosa*—a bacterium naturally present on the skin. Topical treatment with live *R. mucosa* was safe for adults and children with eczema and was associated with reduced disease severity. Final results from this NIAID study will provide the foundation for larger trials to evaluate the efficacy of the novel investigational therapy.[1941–1944]

NIAMS intramural researchers have also expanded previous work by determining that higher levels of one particular bacteria on the skin—*S. aureus*, which causes staph infections—leads to the development and progression of eczema. Extramural researchers funded by NIAMS have translated basic understanding of

[1939] http://www.infectiousdiseasesonline.com/event/workshop/hiv-microbiome-workshop-2017/?utm_campaign=website&utm_source=sendgrid.com&utm_medium=email.
[1940] Ma C, et al. *Science* 2018;360(6391):eaan5931. PMID: 29798856.
[1941] https://www.niaid.nih.gov/news-events/bacteria-therapy-eczema-shows-promise-nih-study.
[1942] https://www.niaid.nih.gov/diseases-conditions/eczema-atopic-dermatitis.
[1943] https://www.clinicaltrials.gov/ct2/show/NCT03018275.
[1944] Myles IA, et al. *JCI Insight* 2018;3(9):120608. PMID: 29720571.

the skin microbiome to develop a new therapeutic intervention, a probiotic lotion, designed to help reduce the abundance of the harmful bacteria and restore the skin microbiome to a normal state.[1945– 1948]

Furthermore, investigators are studying the oral microbiome to understand how different communities of bacteria interact and function within the mouth and how interventions might treat resulting problems. By analyzing the distinct interactions between bacteria in the mouth, scientists aim to develop a probiotic therapy that would supercharge beneficial bacteria already in the mouth and boost their protective power to prevent dental caries. Researchers conducted a study looking at the differences in the oral microbiome between people with many decayed teeth and those with none. They identified a specific strain of bacteria, *A12*, which hinders the activities of *S. mutans*. The researchers are investigating the therapeutic application of a probiotic supplement that contains the *A12* bacteria, which could be taken by mouth to keep harmful bacteria in check and prevent dental caries.[1949,1950]

This research complements yet another approach to eradicating caries by stopping the formation of harmful biofilms before they can contribute to caries development. An NIDCR-supported group of scientists and engineers discovered that an FDA-approved nanoparticle drug, ferumoxytol, could be combined with hydrogen peroxide as an oral rinse to break the molecular bonds that hold together plaque. This discovery has applications beyond oral health, because the mechanism could potentially be used on other biofilms in medicine or industry.[1951]

Minority Health and Health Disparities

More than 327 million people live in the U.S., spread over 3.5 million square miles and with more than 80 percent of the population living in urban areas.[1952] By virtue of our geography alone, there is diversity in health and health practices. This diversity, however, is further enriched by our history as a nation of immigrants. It is estimated that 13.4 percent of the U.S. population are foreign-born, and 11.7 percent are native-born with at least one foreign-born parent. Together, these two groups account for about a quarter of the U.S. population.[1953,1954] African Americans account for 13.4 percent of the population, Hispanic or Latino individuals for 18.1 percent, Asian Americans for 5.8 percent, and AI/AN for 1.3 percent—to mention only a few of the resident racial and ethnic groups in U.S.

[1945] https://directorsblog.nih.gov/2017/03/07/eczema-relief-probiotic-lotion-shows-early-promise/.
[1946] https://www.niams.nih.gov/newsroom/spotlight-on-research/role-microbiota-eczema-findings-suggest-striking-right-balance-keeps.
[1947] Byrd AL, et al. *Sci Transl Med* 2017 Jul 5;9(397):eaal4651. PMID: 28679656.
[1948] Nakatsuji T, et al. *Sci Transl Med* 2017;9(378):eaah4680. PMID: 28228596.
[1949] https://projectreporter.nih.gov/project_info_description.cfm?aid=9422604&icde=43093507.
[1950] Huang X, et al. *Caries Res* 2018;52(1-2):88-101. PMID: 29258070.
[1951] Liu Y, et al. *Nat Commun* 2018 Jul 31;9(1):2920. PMID: 30065293.
[1952] http://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural/ua-facts.html.
[1953] https://www.census.gov/quickfacts/fact/table/US/PST045218.
[1954] https://www.census.gov/content/dam/Census/library/publications/2016/demo/P23-214.pdf.

Minority health research—the scientific investigation of distinctive health characteristics and attributes of minority racial and/or ethnic groups who are underrepresented in biomedical research—is a priority for NIH and is critically important for the health of our nation as a whole. In particular, NIH has devoted considerable resources to health disparities research. A multidisciplinary field of study devoted to gaining greater scientific knowledge about the influence of health determinants and translating this knowledge into interventions to address differences in health outcomes, minority health research aims to provide a better understanding of why certain populations have poorer health outcomes.[1955] Research findings have shown consistently that health disparities can arise from biological differences, as well as exposure to, and behaviors developed within, societal, cultural, and environmental contexts. The result is gradients in health mediated by such factors as physiology, behavior, and gene expression. As a result of these efforts, a complex web of interconnected and overlapping factors influencing health has been identified—informing how health is addressed not only among minority populations, but among all Americans.

Summary of NIH Activities

In keeping with its role as the nation's primary steward of biomedical and behavioral research, NIH is committed to improving minority health and eliminating health disparities in the U.S. at the individual, community, regional, and national levels. NIH-designated U.S. health disparity populations include Black/African Americans, Hispanics/Latinos, Asian Americans, AI/AN, Native Hawaiian and other Pacific Islanders, socioeconomically disadvantaged populations, underserved rural populations, and SGM populations.[1956–1958]

NIMHD is charged with coordinating and leading the NIH vision and programs on minority health and health disparities research—envisioning an America in which all populations will have an equal opportunity to live long, healthy, and productive lives.[1959] In addition, research on minority health and health disparities is conducted and funded throughout the 27 NIH ICs. In FYs 2016–2018, NIH funded $9.5 million in research in health disparities and $8.7 million in minority health research. All ICs at NIH fund some research in minority health or health disparities. As such, coordinating offices, such as the THRO and the SGMRO, facilitate dialogue and exchange between Institutes.

Established in 2015, THRO is located in the DPCPSI in the OD.[1960] The office was created in recognition of the importance of ensuring meaningful input from and collaboration with tribal Nations on NIH programs and policies. THRO functions include coordination and communication, as well as convening events and activities related to tribal health research and scientific priorities for AI/AN.

[1955] https://hdpulse.nimhd.nih.gov/.
[1956] https://www.nimhd.nih.gov/about/overview/index.html.
[1957] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-089.html.
[1958] In October 2016, NIMHD, in collaboration with AHRQ, announced that SGM populations had been officially designated as a health disparity population for NIH and AHRQ research: https://grants.nih.gov/grants/guide/notice-files/NOT-MD-19-001.html.
[1959] https://www.nimhd.nih.gov/about/overview/mission-vision.html.
[1960] https://dpcpsi.nih.gov/thro.

Also established in 2015 and situated within DPCPSI, SGMRO coordinates SGM-relevant research and activities by working directly with NIH ICOs.[1961]

SGM populations include, but are not limited to, individuals who identify as lesbian, gay, bisexual, asexual, transgender, two-spirit, queer, and/or intersex. Individuals with same-sex or -gender attractions or behaviors and those with a difference in sex development (DSD) are also included. These populations also encompass those who do not self-identify with one of these terms but whose sexual orientation, gender identity or expression, or reproductive development is characterized by non-binary constructs of sexual orientation, gender, and/or sex.

The work funded by NIH spans projects that seek to better understand minority health and health disparities, including where disparities exist and how they arise, as well as to develop and refine interventions to address these health disparities.

Updates on some of NIH's activities relating to minority health and health disparities are outlined in this section. Additional work relating to minority health and health disparities, as it pertains to specific health areas, is illustrated in other sections of this chapter as appropriate, and a full update on the NIMHD Centers of Excellence is presented in Chapter 4.

Understanding Minority Health and Health Disparities

NIH has funded research on minority health and health disparities in a range of areas, including many chronic conditions, such as sleep, kidney disease, and cardiovascular disease, to name just a few.

In the U.S., 30 to 40 percent of adults and 40 to 70 percent of adolescents report sleep deficiencies. Racial and ethnic minorities and health disparity populations have the highest prevalence of sleep deficiency and are more likely than Whites to have persistent and underdiagnosed poor sleep quality.[1962] Yet the underlying factors and the mechanisms contributing to disparities in healthy sleep are not well understood. In FY 2018, NIMHD initiated the Mechanisms and Consequences of Sleep Disparities in the U.S. Program to promote research to understand the underlying social, cultural, environmental, or biological factors that contribute to sleep deficiencies among racial and ethnic minority and health disparity populations and to understand how sleep deficiencies may lead to disparities in health outcomes. The research portfolio covers a range of potential mechanisms and health outcomes—including sleep and circadian mechanisms—to help explain health risk behaviors like smoking and such health outcomes as hypertension, cognitive impairment, chronic obstructive pulmonary disease, and postpartum weight gain. One of the many important areas being examined includes the reciprocal relationship of racial discrimination on sleep and cardiovascular functioning.

Research co-funded by NIEHS examined a novel biomarker of cardiovascular disease in participants from 20 Navajo communities participating in the Diné Network for Environmental Health Project. The project seeks to understand the long-term public health and environmental effects of more than 50 years of

[1961] https://dpcpsi.nih.gov/sgmro.
[1962] https://grants.nih.gov/grants/guide/pa-files/PAR-17-235.html.

uranium mining on the Navajo Nation. Type 2 diabetes, hypertension, and obesity are prevalent in this Navajo population, and scientists have found abnormal levels of cardiovascular disease biomarkers, suggesting this population is facing disparities in cardiovascular disease risk as well.[1963]

Risk of cardiovascular disease is further exacerbated by childhood obesity, which is itself a public health concern in the U.S., particularly among AI/AN children. An NICHD-funded study aims to assess the obesity prevention intervention from the Family Spirit Nurture study, which incorporates infant and young child feeding practices and physical activity among members of the White Mountain Apache Tribe and the Navajo Nation. NICHD-supported researchers will assess maternal feeding practices and behaviors, infant and toddlers' diets, levels of physical activity, and BMI from birth to 2 years of age. In 2017, the team met with the study communities and began engaging in recruitment.[1964]

Chronic kidney disease is also a growing public health concern—one that disproportionately affects African Americans, who are two to four times more likely to develop end stage renal disease (ESRD) than Whites in the U.S. Funded by NHLBI, an analysis from the Jackson Heart Study found that over 10 years, 12 percent of study participants exhibited a rapid decline in kidney function. Such individuals were older and were more likely to be of low or middle income, have diabetes, and have higher systolic blood pressure than those with less rapid decline. These findings suggest that interventions targeting potentially modifiable factors—such as smoking, alcohol use, diet, and physical activity—may help reduce the incidence of kidney failure.[1965] These types of findings are relevant for understanding the disparities in health between African Americans and Whites, and they also increase our understanding of ESRD overall.

Thus, identifying subpopulations where health and disease processes differ is important, not only for understanding and addressing disparities but for arriving at a deeper understanding of the progression of disease in all populations. For example, osteoporosis and low bone mass are common in older Puerto Ricans. Data suggest that osteoporosis risk, fracture rates, and the cost of treatment are increasing in the Hispanic population. However, these studies have focused mainly on Mexican Americans despite evidence that Hispanic subgroups have different rates of bone loss. Now, data from the Boston Puerto Rican Osteoporosis Study funded by NIAMS suggest that Puerto Rican and non-Hispanic White women have similar rates of osteoporosis and that the middle-aged Puerto Rican men in this study are more likely to have osteoporosis than older Puerto Rican men. This finding is important because understanding osteoporosis and low bone mass in different populations will allow better screening, diagnosis, and treatment that can lead to decreased overall costs and improved quality of life for those at risk for or with disease.[1966]

Along a similar vein, a study examining cognition among older individuals with HIV showed that a greater frequency of cognitive activity was associated with better global cognition, episodic memory, working memory, and perceptual speed only among African Americans. Although older persons with HIV are at

[1963] Harmon ME, et al. *PLoS One* 2016;11(3):e0143102. PMID: 26938991.
[1964] https://projectreporter.nih.gov/project_info_details.cfm?aid=9406321&icde=42106153.
[1965] Young BA, et al. *Am J Kidney Dis* 2016;68(2):229-239. PMID: 27066930.
[1966] Noel SE, et al. *J Bone Miner Res* 2018;33(3):396-403. PMID: 29044768.

risk for impaired cognition, limited information had previously been available on modifiable factors associated with neurocognitive function.[1967]

It is well established that individuals with one chronic condition may have additional chronic conditions or be at increased risk of developing other conditions. Among disparities populations, this compounded burden further complicates the landscape.

The MESA, funded by NHLBI, aims to enable investigators to study CVD alongside other complex and chronic diseases. MESA researchers originally measured the amount of coronary artery calcium (CAC) in participants' blood vessels because CAC is a well-known predictor of heart disease and stroke. However, when looking at data from more than 6,800 MESA participants followed over about 10 years, researchers also found that participants with a high CAC score were at increased risk of cancer, chronic kidney disease, COPD, and hip fractures.[1968,1969]

Figure 115. "National Wear Red Day": Infographic. NHLBI.

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is the largest epidemiological study on Hispanic/Latino health in the U.S., with approximately 16,500 participants in Chicago, Miami, New York City, and San Diego. Led by NHLBI in collaboration with six other NIH Institutes, the study primarily seeks to define the prevalence of risk factors for cardiovascular and lung diseases and how these risk factors affect future cardiovascular and pulmonary events among diverse Hispanic/Latino groups. In 2018, the researchers reported finding several genes that are associated with lung function and COPD in this population. The findings have the potential to advance our understanding of the mechanisms of lung disease and unique therapeutic approaches in Hispanic/Latino populations.[1970–1972]

Behaviors, particularly health-related behaviors, are also health outcomes in themselves. As such, they are also an active area of study in minority health and health disparities research.

[1967] Krueger KR, et al. *AIDS* 2017;31(3):437-441. PMID: 27835616.
[1968] https://www.mesa-nhlbi.org/.
[1969] Handy CE, et al. *JACC Cardiovasc Imaging* 2016;9(5):568-576. PMID: 26970999.
[1970] https://www.nhlbi.nih.gov/research/resources/obesity/population/hchs.htm.
[1971] https://sites.cscc.unc.edu/hchs/StudyOverview.
[1972] Burkart KM, et al. *Am J Respir Crit Care Med* 2018;198(2):208-219. PMID: 29394082.

An analysis from the Jackson Heart Study found the strongest evidence to date that regular moderate-to-vigorous exercise can help reduce the risk of hypertension in African Americans. The analysis involved participants who were in their late 40s and who did not have hypertension when the study began. They were followed for 8 years and surveyed about their physical activities throughout. At the end of follow-up, the researchers found that nearly 50 percent of the participants had developed hypertension. However, those who reported higher levels of moderate to vigorous physical activity had a significantly lower risk of hypertension (a 16 to 24 percent lower rate, depending on exercise level) compared with those who did not exercise at all.[1973,1974]

To broadly examine this health behavior, NHLBI funded a study examining parent–child pairs who were of low income and participating in two ongoing obesity prevention clinical trials. They found that parents' physical activity—and their sedentary behavior—directly correlated with the activity level of their preschoolers. Among the study participants, 75 percent were Latino and almost 10 percent were African American.[1975]

Among other behaviors that have been studied are what is termed *health-seeking behaviors*. Mexican Americans are at higher risk for oral diseases, such as caries, gingivitis, and chronic periodontitis. By analyzing oral health care use patterns of hundreds of Mexican Americans, researchers identified specific characteristics of the social network that impact the knowledge and access to oral health services of individuals. They found that individuals who have social networks that include others with comparatively higher levels of schooling sought oral care, including preventive services, more frequently. Interestingly, this held true regardless of the person's own level of education.[1976]

A person's social networks have also been found to be important in other areas of health. A study funded by NIMHD assessed the association between e-cigarette exposure and tobacco marketing on cigarette smoking exposure, acceptance of cigarette smoking, and susceptibility to cigarette smoking among vulnerable populations. They found that a participant's own use of an electronic nicotine delivery system (ENDS), exposure to ENDS advertising, and living with ENDS users were associated with acceptance of adult cigarette smoking even among never smokers. Youth ENDS exposure may contribute to normalizing adult cigarette smoking and may, in turn, heighten susceptibility to cigarette smoking. Further longitudinal studies are necessary to determine whether ENDS policy interventions can help to prevent youth cigarette smoking.[1977]

In May 2018, a NIDA-funded study was published using data from the Monitoring the Future (MTF) study, which found that lifetime drug use and 40-day rates of use were higher among American Indian youth

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[1973] https://www.nhlbi.nih.gov/news/2017/nih-study-shows-exercise-may-lower-risk-high-blood-pressure-african-americans.
[1974] Diaz KM, et al. *Hypertension* 2017;69(3):421-427. PMID: 28137988.
[1975] Barkin SL, et al. *Am J Prev Med* 2017;52(4):424-432. PMID: 28081998.
[1976] Maupome G, et al. *Community Dent Oral Epidemiol* 2016;44(6):540-548. PMID: 27477831.
[1977] Choi K, et al. *J Adolesc Health* 2017;60(5):592-598. PMID: 28159423.

than among the general MTF sample at each grade level for nearly all illicit substances.[1978,1979] This is a particular problem because drug overdose deaths are a public health concern across all racial and ethnic groups.

Although opioid use presents a significant public health problem, a study published in December 2017 by researchers at NIDA and NCI showed that cocaine is also a consistent contributor to overdose deaths. The research suggests that rates of cocaine-related overdose deaths in the non-Hispanic Black population are similar to heroin-related deaths among non-Hispanic White women and prescription opioid-related deaths among non-Hispanic White men.[1980,1981]

Health disparities exist not only in terms of chronic conditions and health behaviors, but also in exposure to violence. In the U.S., more than 27 percent of women and 11 percent of men have experienced sexual violence, physical violence, and/or stalking by an intimate partner in their lifetime and experienced an intimate partner violence-related impact. NICHD-supported researchers recently reported a high prevalence of intimate partner violence over a 5-year period among a representative sample of families living in rural, low-income communities in eastern North Carolina and central Pennsylvania. To better understand the potential cause, researchers surveyed and visited families that recently had a new baby, beginning when the child was 6 months old and continuing periodically through the child's fifth year. Depending on the timing of these visits, between 21 percent to 41 percent of couples reported intimate partner violence—generally higher than national rates. Violence was most prevalent around the time of the birth of the child, decreasing significantly over the following five years.[1982]

Identifying How Health Disparities Arise

To better understand why health disparities exist and therefore how to address them, NIH has funded research to understand the causes of disparities. The NIMHD Minority Health and Health Disparities Research Framework provides a means to consider mechanisms at the personal or individual, interpersonal, community, and societal levels. Each level may have associated biological, behavioral, environmental, or sociocultural factors or factors related to treatment within or access to the health care system. Furthermore, the different levels and domains may interact with one another. In the model, health outcomes can span multiple levels; the model also includes a life-course perspective that emphasizes the importance of factors ranging across the lifespan in determining health disparities.[1983] For example, individuals may have genetic differences that subject them to increased risk of disease but only when they are exposed to certain contaminants in the environment. This exposure may occur early in life,

[1978] https://www.drugabuse.gov/news-events/news-releases/2018/05/higher-rate-substance-use-among-native-american-youth-reservations.
[1979] Swaim RC, et al. *JAMA Netw Open* 2018;1(1):e180382. PMID: 30646057.
[1980] https://www.drugabuse.gov/news-events/news-releases/2017/12/cocaine-contributes-to-overdose-deaths-among-some-minorities.
[1981] Shiels MS, et al. *Ann Intern Med* 2018;168(6):453-455. PMID: 29204603.
[1982] Gustafsson HC, et al. *J Fam Violence* 2016;31(1):49-60. PMID: 26709334.
[1983] https://www.nimhd.nih.gov/about/overview/research-framework/.

but the disease itself may not manifest until much later in life. Thus, the body of research to understand the cause of disparities varies greatly and can be quite complex.

Illustrating that complexity, NIA has been conducting the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, an interdisciplinary, community-based, longitudinal epidemiologic study of socioeconomically diverse African Americans and Whites residing in Baltimore, Maryland. HANDLS studies have identified perceived discrimination as a psychological stressor that influences self-reported health, systemic arterial hypertension, obesity, and cardiovascular reactivity, among other conditions. NIA IRP investigators have transitioned to examining the underlying biological processes through which discrimination is transformed into disease or affects the presence of age-related disease biomarkers. To date, work on the HANDLS Discrimination Initiative suggests that perceived discrimination deserves further investigation as a psychosocial risk factor for kidney disease, poor brain health, and perhaps accelerated aging.[1984– 1990]

Another large-scale study, the Coronary Artery Risk Development in Young Adults (CARDIA) study, is an NHLBI-funded long-term study of cardiovascular risk factors enrolling more than 5,000 Black and White women and men from Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Participants have undergone clinical tests and completed questionnaires at 5-year intervals for 25 years. A recent evaluation of the place and history of residence and history of high blood pressure of more than 2,000 CARDIA participants found that, in Black participants, reductions in systolic blood pressure over 25 years were associated with less racial segregation in participants' place of residence.[1991,1992]

Similar results were found for type 1 diabetes, where neighborhood disadvantage was observed to be associated with poor metabolic control among African Americans. An NIMHD-funded study examined the impact of neighborhood disadvantage on inflammation and poor metabolic control in a racially diverse population of pediatric patients with type 1 diabetes. The study identified an association between neighborhood disadvantage and poor metabolic control among African Americans who had a higher hemoglobin A1c (HBa1c) level than Whites, as well as a link with inflammation among both African Americans and Whites. The findings point to the need for more research to improve understanding of the relationship between social determinants of health and pediatric diabetes.[1993]

This effect is also felt by Hispanics or Latinos, who are almost twice as likely as Whites to have diabetes. Studies have shown an association between poor diabetes outcomes and negative psychosocial factors,

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[1984] Beatty Moody DL, et al. *Biol Psychol* 2019;141:1-9. PMID: 30553820.
[1985] Beatty Moody DL, et al. *Health Psychol* 2019;38(1):63-74. PMID: 30474995.
[1986] Pantesco EJ, et al. *Psychoneuroendocrinology* 2018;98:119-126. PMID: 30138832.
[1987] Beydoun MA, et al. *Psychosom Med* 2017;79(7):824-834. PMID: 28445210.
[1988] English D, et al. *Am J Community Psychol* 2014;54(3-4):219-28. PMID: 24969707.
[1989] Sutin AR, et al. *Nicotine Tob Res* 2014;16(6):794-9. PMID: 24477195.
[1990] Szanton SL, et al. *Int J Behav Med* 2012;19(4):489-95. PMID: 21913047.
[1991] https://www.cardia.dopm.uab.edu/.
[1992] Kershaw KN, et al. *JAMA Intern Med* 2017;177(7):996-1002. PMID: 28505341.
[1993] Coulon SJ, et al. *Pediatr Diabetes* 2017;18(2):120-127. PMID: 26783014.

such as stress. Researchers examined the efficacy of a community health worker (CHW)-delivered stress management intervention compared to CHW-delivered diabetes education on mental health and diabetes outcomes in Hispanic or Latino adults with type 2 diabetes. Participants receiving stress management had greater improvements in depression, anxiety, and self-reported health status. Diabetes outcomes (HBa1c, diabetes distress, urinary cortisol) showed no significant group effects. However, increasing attendance at stress management sessions was associated with greater improvements in HbA1c and diabetes distress.[1994]

NICHD-supported researchers have also analyzed the mortality differences between infants born to White, African American, Mexican, Puerto Rican, Asian, and Native American mothers and examined demographic and economic factors, race, and country of birth. Differences between most groups were associated with economic factors, including maternal marital status, education, and age, which were also strong predictors of income and poverty, according to U.S. Census data. The gap between Black and White populations, as well as the gap between Puerto Rican and White populations, occurred at low birth weights, while the gap between Native American and White populations occurred almost exclusively at high birth weights. The researchers also found that infants born to Mexican mothers die at relatively low rates compared to others at the same socioeconomic level, which was attributed to the mothers' being foreign-born.[1995]

In a study funded by NHLBI, researchers gathered data from more than 12,000 participants in the HCHS, MESA, and the Starr County Health Study and found several genes associated with the severity of sleep apnea in Hispanic/Latino Americans.[1996] However, another study examining children in six communities in the U.S., found greater sleep apnea severity among children who were African American, poor, or living in single-parent households. Notably, poverty was the strongest risk factor.[1997]

Measures of socioeconomic status (SES)—such as individual or family income, poverty, education, neighborhood measures, or housing quality—are concepts that are highly interrelated with one another. They can be measured for individuals or measured and conceptualized at a community or group level as well. Research has shown that they are important to understand in characterizing health disparities. Furthermore, they are related to an individual's ability to access high-quality health care.

A new tool supported by NIMHD and NIA, the *Neighborhood Atlas*, was established in 2018 to help researchers visualize socioeconomic data at the community level. A neighborhood's socioeconomic measures—such as income, education, employment and housing quality—may provide clues to the effects of those factors on overall health and could inform health resources policy and social interventions.[1998]

[1994] Wagner JA, et al. *Diabetes Res Clin Pract* 2016;120:162-70. PMID:27568646.
[1995] Elder TE, et al. *Labour Econ* 2016;43:42-54. PMID: 27695196.
[1996] Cade BE, et al. *Am J Respir Crit Care Med* 2016;194(7):886-897. PMID: 26977737.
[1997] Wang R, et al. *Ann Am Thorac Soc* 2017;14(1):76-84. PMID: 27768852.
[1998] Kind AJH, et al. *N Engl J Med* 2018;378(26):2456-2458. PMID: 29949490.

Another source of information regarding where barriers to access might exist is electronic medical records (EHR). To highlight recent innovative application and ongoing research, OBSSR supported a 1-day workshop titled *Screening and Referral for Social Determinants of Health: Innovative Health Care Applications and Future Directions*. The workshop was held in May 2018 in collaboration with AHRQ, CMS, HRSA, and VA, and presentation topics spanned current opportunities and challenges for the collection and use of social determinants in screening and referral, research innovations in social determinants of screen and referral, and scientific evidence to inform policy and practice in diverse patient populations. This workshop facilitated dialogue regarding future research directions among scientific researchers in the field, staff at NIH, and representatives from other federal agencies.[1999,2000]

Beyond access to care, however, the quality and level of treatment may also differ across populations. Many adults have BP readings that are elevated in a clinical setting, but lower when measured outside the clinic, a phenomenon known as the *white-coat effect*. An analysis from the Jackson Heart Study, funded by NHLBI, found that the white-coat effect was larger among African Americans 60 years and older than those younger than 60 years and was larger for all study participants without diabetes or chronic kidney disease, regardless of age. This is concerning because older adults and patients with chronic disease with white-coat high blood pressure may be over-treated and thus be susceptible to the adverse effects of low BP, such as injuries from serious falls.[2001]

An NICHD-funded study examined disparities in pain treatment for children with appendicitis, reviewing a national database of medical records for nearly 1 million emergency department visits by children who were diagnosed with appendicitis. The researchers found that appendicitis pain appeared to be under-treated, with only 57 percent of children receiving any pain medication. Black children were less likely than White children to receive any pain medication for moderate pain and less likely to receive opioids for severe pain.[2002]

Of course, appropriate care cannot be obtained without an appropriate diagnosis—yet another area where disparities exist. Socioeconomic, racial, and ethnic disparities in ASD exist among U.S. children alongside an overall doubling of the prevalence of ASD in the U.S. between 2002 and 2010. Researchers analyzed population-based surveillance, census, and survey data and found that the overall prevalence of ASD was highest among non-Hispanic White, next highest among non-Hispanic African American, and lowest among Hispanic populations. Although the prevalence of ASD has increased over time with greater prevalence among those with higher SES, investigators found racial and ethnic disparities in ASD prevalence persisted even within SES levels and were especially pronounced among children in low-SES communities. Consistent with prior research that suggests low prevalence is indicative of under-diagnosis of ASD, this finding suggests that the negative effects of poverty on ASD diagnosis are compounded by further under-diagnosis among African Americans and Hispanics.[2003]

[1999] https://www.scgcorp.com/SocialDeterminants18/Default.
[2000] https://videocast.nih.gov/summary.asp?Live=27331&bhcp=1.
[2001] Tanner RM, et al. *J Clin Hypertens* 2016;18(2):139-45. PMID: 26279070.
[2002] Goyal MK, et al. *JAMA Pediatr* 2015;169(11):996-1002. PMID: 26366984.
[2003] Durkin MS, et al. *Am J Public Health* 2017;107(11):1818-1826. PMID: 28933930.

Complementary studies shed light on why differences to access and diagnosis might occur across different settings, including oral health, ED treatment, mental health services, and surgical care. Studies funded by NIMHD examined potential ED provider bias and its association with care for AI/AN children. A survey of care providers at five hospitals measured implicit and explicit bias toward children and caregivers in the ED and found that 84 percent of clinicians had an implicit preference for White adults or children. In addition, the greater the number of AI/AN children seen in the ED, the more clinicians saw AI/AN children as challenging and caregivers as less compliant. Further research should determine how ED clinician biases influence health care or outcomes disparities and what types of interventions can be created to reduce this disparity.[2004]

Specifically, for injuries and post-injury care in AI/AN and rural patients, NICHD researchers found that a significantly higher percentage of AI/AN individuals were hospitalized for intentional and unintentional injuries compared with non-Hispanic White individuals. Further compounding the burden, AI/AN patients were most likely to be discharged to their own homes without home health services.[2005] Data from another NICHD-funded study showed that, compared to urban children, rural children with mild TBI were more likely to use physical therapy or occupational therapy (PT/OT) services, but less likely to use speech therapy or mental health services than their urban peers. Total health care costs were higher for rural children due mainly to the higher costs of PT/OT.[2006]

This extends to other areas of health, as well including perceived discrimination in mental health of substance misuse treatment services. Investigators funded by NIMHD examined the association between perceived discrimination in mental health or substance use, participants' rating of treatment helpfulness, and timing of treatment termination. Researchers analyzed data from the California Quality of Life Survey for more than 1,000 adults with prior-year visits for mental health or substance use. Four percent of adults reported discrimination during mental health or substance use visits, with uninsured patients being seven times more likely to report discrimination compared with other groups. The most commonly cited cause of discrimination as attributed by participants was race and ethnicity for both African Americans (52 percent) and Hispanics or Latinos (31 percent). In comparison, the most common cause among Whites was insurance status (40 percent). Discrimination experience was associated with negative mental health or substance use for Hispanics or Latinos and Whites. In contrast, for African Americans, discrimination experience was associated with early treatment termination.[2007]

To understand disparities with respect to surgical treatment, NIMHD established the Surgical Disparities Research Program, launched in FY 2016 in collaboration with NCI, NIAMS, ORWH, NINR, NICHD. This initiative will seek to understand disparities and identify multilevel strategies at the institutional and systems level that may reduce disparities. Building on recommendations from a workshop convened at NIH in collaboration with the American College of Surgeons, NIMHD issued two new FOAs in FY 2016 soliciting applications for research project grants on Surgical Disparities Research and

[2004] Puumala SE, et al. *Med Care* 2016;54(6):562-9. PMID: 26974675.
[2005] Fuentes MM, et al. *J Racial Ethn Health Disparities*. 2019 Apr;6(2):335-344. PMID: 30276637.
[2006] Graves JM, et al. *Health Serv Res*. 2019;54(2):337-345. PMID: 30507042.
[2007] Mays VM, et al. *Med Care* 2017;55(2):173-181. PMID:27753743.

Exploratory/Developmental Surgical Disparities Research. The Developing Disparities-Sensitive Surgical Quality Metrics is an example of a surgical disparities research project aimed at developing a standardized disparities-sensitive metric on quality of surgical care that can be implemented in various hospital settings. Another project has also been undertaken to examine the use of opioid pain medication in children after surgery, to enhance understanding of the relationship between racial disparities in post-surgery pain management and opioid addiction.[2008]

NIH has also funded research to understand the challenges facing those with disabilities. A recently renewed initiative will support research investigating the incidence, course, and outcomes of pregnancy among women with disabilities. Areas of interest include preconception care and antenatal counseling, management of pregnancy, prenatal care, and the transition to parenthood.[2009]

Among disparities populations, even when access and quality of care are addressed, variation in measurements still exists, which may present challenges. For example, standards for fetal anthropometric (body measurement) parameters, measured longitudinally throughout gestation, are pivotal to understanding the dynamics of human fetal growth and to defining normal and abnormal fetal growth. Fetal growth measurements are used to determine whether a pregnancy is healthy and progressing because appropriate growth influences health and well-being even as infants grow into childhood, through to adolescence and beyond. However, normal variation in body size, particularly across racial and ethnic groups, makes the use of standards across groups potentially problematic. The NICHD Fetal Growth Studies followed a diverse cohort of women, including an obese cohort and a twin cohort, where study participants underwent five ultrasounds during pregnancy at different gestational ages, along with nutritional assessments, body measurements, and analysis of blood samples.[2010] This research was conducted at NIH and found that because of racial and ethnic differences in normal growth patterns the current standards used in obstetric care may misclassify the fetuses of minority mothers as being too small in up to 15 percent of fetuses.[2011] Although some research suggests that stress levels among low-risk pregnant women did not affect newborn growth,[2012] inaccurate standards may nevertheless lead to unnecessary tests and stress for these minority women when their pregnancies actually remain on track.

The causes of disparities are complex and go well beyond treatment and health care. One area of research within the biological domain of disparities is genetic differences, with results in a variety of disease areas. Researchers funded by NIMHD with support from NIDDK identified genetic links to kidney disease in African Americans. People of recent African ancestry develop CKD and end stage kidney failure at rates five times that of Whites. Although two variants in the *APOL1* gene account for disproportionately high kidney failure rates in African Americans, the underlying mechanisms are poorly understood. Investigators examined this in kidney cells that contained these gene variants and found that changes in signaling within

[2008] https://grants.nih.gov/grants/guide/pa-files/PAR-16-391.html.
[2009] https://grants.nih.gov/grants/guide/pa-files/PA-17-452.html.
[2010] https://www.nichd.nih.gov/about/org/diphr/officebranch/eb/fetal-growth-stud.
[2011] Buck Louis GM, et al. *Am J Obstet Gynecol* 2015;213(4):449.e1-449.e41. PMID: 26410205.
[2012] Wing DA, et al. *Am J Obstet Gynecol* 2017;217(1):82.e1-82.e7. PMID: 28263750.

cells occurred. These changes in signaling are understood to cause cells to swell and die, reflecting a mechanism by which the *APOL1* gene variants may be causing kidney failure.[2013]

Figure 116. New NIH awards accelerate the use of clinical genomics in diverse and underserved populations. Credit: Ernesto Del Aguila III, NHGRI.

African American patients have higher rates of stroke and venous thromboembolism and are at higher risk of major bleeding from warfarin compared to White patients. Four newly identified SNPs were found to be associated with increased risk of major bleeding among patients of African descent taking warfarin. A NIMHD study identified a novel association of a haplotype, or set of genes inherited from a single parent, in patients of African descent with an increased risk of major bleeding while taking warfarin. The associated SNPs were found to be relatively common in persons of African descent in the 1000 Genomes Project.[2014]

New genetic markers were also identified for glaucoma, a progressive blinding disease marked by increasing fluid pressure in the eye and one of the leading causes of blindness in the U.S. African Americans are particularly vulnerable to glaucoma, which affects them more severely and at earlier ages than non-minority populations. The African Descent and Glaucoma Evaluation Study (ADAGES) III study, funded by NEI and currently the third ADAGES study to date, examined African American patients for genetic markers that could provide insight into their increased susceptibility to disease. In a large study with more than 3,000 African American participants, the ADAGES III team identified a new genetic marker in African American glaucoma patients. The team will continue to work on understanding how this genetic marker could increase disease risk.[2015]

In an effort to identify potentially explanatory genetic differences on a broader scale, researchers funded by NIDCR performed a GWAS on DNA from the HCHS/SOL. In this case, investigators aimed to determine how an individual's genes affect the development of dental caries, which are more common in underserved and minority populations. They identified two genes associated with dental caries in Hispanic adults: *NAMPT*, which is involved in periodontal healing, and *BMP7*, a gene involved in tooth and bone

[2013] Olabisi OA, et al. *Proc Natl Acad Sci USA* 2016;113(4):830-7. PMID:26699492.
[2014] De T, et al. *JAMA* 2018;320(16):1670-1677. PMID: 30357299.
[2015] Taylor KD, et al. *Ophthalmology* 2019;126(1):38-48. PMID: 30352225.

development. Additional studies will verify these associations and explore the possibilities of personalizing caries prevention and treatment.[2016,2017]

Within the context of medical research, the objective of identifying genetic variants is to influence disease risk, potentially making that information useful in a clinical setting. The Clinical Sequencing Evidence-Generating Research Program, which began in FY 2018, is the second phase of NHGRI's effort to assess the usefulness of clinical genome sequencing and to facilitate the integration of genomic, clinical, and health care data in real-world settings and inform clinical decision-making. In this second phase, at least 60 percent of research participants will be from underserved and underrepresented populations, allowing assessment of barriers to using genome sequencing in a broad range of clinical settings.[2018]

Genetic information, however, is also used in other contexts. The NIH CC, THRO, and NHGRI together examined genetic profiles within the context of AI/AN ancestry and consumer ancestry testing. Although genetic ancestry tests are often characterized as recreational, companies invoke deeply personal concepts of individual identity, group membership, and kinship when marketing their services. In particular, many companies claim to be able to determine AI/AN heritage, claims that are not supported by the state of the science and may have significant cultural and political consequences for U.S. tribal communities. These claims regarding genetic ancestry, personal identity, and cultural membership are problematic and challenge how U.S. tribal Nations currently identify and create potential obstacles for tribal sovereignty.[2019]

Although genetic makeup may explain a degree of differences in risk of disease, response to treatments and to environmental exposures may also differ because of our genes. As an example, low to moderate exposure to arsenic, such as that found in well water, is associated with an increased risk for CVD and stroke in AI/AN individuals. Researchers with NHLBI's Strong Heart Study also found that low to moderate arsenic exposure is associated with type 2 diabetes and insulin resistance. Given that arsenic metabolism and toxicity differ from person to person, researchers conducting the Strong Heart Study have looked for gene variations that might explain these differences. They found that individuals with certain variations in the *AS3MT* gene are more likely to have metabolic signs of arsenic toxicity.[2020– 2023]

This type of differential response to environmental exposures, termed gene–environment interaction, is a mechanism by which health disparities may manifest. As such, a deeper understanding of these interactions would improve our ability to influence health outcomes in meaningful ways. NIMHD's Social Epigenomics Initiative offers a unique opportunity to understand how exposures from the environment, diet, lifestyle, and other health determinants interact with our genes to influence minority health and

[2016] Morrison J, et al. *Hum Mol Genet* 2016;25(4):807-16. PMID: 26662797.
[2017] Sanders AE, et al. *J Dent Res* 2017;96(1):64-72. PMID: 27601451.
[2018] https://www.genome.gov/27546194/.
[2019] Walajahi H, et al. *Genet Med* 2019;21(8):1744-1750. PMID: 30662065.
[2020] http://www.nhlbi.nih.gov/science/strong-heart-study-shs.
[2021] https://strongheartstudy.org.
[2022] Grau-Perez M, et al. *Environ Health Perspect* 2017;125(12):127004. PMID: 29373862.
[2023] Balakrishnan P, et al. *Environ Health Perspect* 2017 ;125(1):15-22. PMID: 27352405.

health disparities in diseases and conditions ranging from pre-term birth to emotional well-being in children, asthma, obesity, cardiovascular disease, prostate cancer, and post-traumatic stress disorder. The Social Epigenomics Research Focused on Minority Health and Health Disparities Initiative, led by NIMHD with contributions from NCI and NIA, supports cutting-edge interdisciplinary research on epigenomic variations within and between health disparity populations. Epigenetic modifications, such as DNA methylation, do not change our genes but can control how genes are "read." Social epigenomics examines how social experiences affect human gene function and physiology. For example, racial discrimination and other social stressors may alter the epigenome, affecting gene expression in ways that may, in turn, alter disease risk or severity. The Initiative promotes novel interdisciplinary collaborations between social and behavioral scientists, clinicians, public health researchers, and molecular biologists to advance understanding of biological and behavioral mechanisms underlying health disparities.[2024]

In addition to potentially different response to the environment, disparities populations may also be more likely to be at risk of being exposed to things that adversely affect health. NIEHS co-funded researchers examined long-term exposure to air pollution and mortality in a large cohort of Medicare beneficiaries. Although evidence of adverse health effects related to air pollution exposure was seen within the entire Medicare cohort, racial minorities and people with low income were disproportionately affected.[2025]

As such, research conducted at the five Centers of Excellence on Environmental Health Disparities is critically important—combining basic and translational research and community involvement to improve understanding of environmental health disparities, as well as identify mitigation and prevention strategies to decrease public health burden.[2026]

NIEHS also funds the Center for Urban Responses to Environmental Stressors (CURES) to understand the health impacts of environmental exposures to complex chemical and non-chemical contaminants in Detroit's urban landscape, which is home to a racially and ethnically diverse population. Recent studies of a small cohort of older African Americans suggests a link between living in poor neighborhoods and increased hair cortisol, which indicates sustained stress.[2027,2028]

Varying methods are used by investigators to understand different facets of health, chronic disease, and behavior. Although some natural occurrences can cause devastation, they can also be an opportunity to study facets of health and its determinants from a different perspective. Unprecedented and widespread damage from Hurricanes Irma and Maria devastated the U.S. territories of Puerto Rico and the U.S. Virgin Islands in 2017. Individuals in this region experienced collective territory-wide disruptions, as well as individual, family, and community-level hardships that may make recovery from these disasters particularly difficult. In FY 2018, through a collaboration with seven other NIH Institutes, NIMHD developed the Time-Sensitive Research on Health Risk and Resilience after Hurricanes Irma and Maria in

[2024] https://www.nih.gov/news-events/news-releases/nih-establishes-new-research-social-epigenomics-address-health-disparities.
[2025] Di Q, et al. *N Engl J Med* 2017;376(26):2513-2522. PMID: 28657878.
[2026] https://www.niehs.nih.gov/research/supported/centers/ehd/index.cfm.
[2027] https://tools.niehs.nih.gov/portfolio/index.cfm/portfolio/grantDetail/grant_number/P30ES020957.
[2028] Zilioli S, et al. *Psychoneuroendocrinology* 2017;80:36-38. PMID: 28315608.

Puerto Rico and the U.S. Virgin Islands Initiative. The program's goal was to examine the health impacts and health risks including onset of acute conditions, exacerbation of existing chronic conditions, and risk for future onset of chronic disease in Puerto Rico and the U.S. Virgin Islands following the physical damage and community-level hardships left by Hurricanes Irma and Maria. A key feature of this initiative was the emphasis on time-sensitive projects because delays in study initiation might preclude addressing certain research questions or the collection of certain types of data. Funded projects included studies on the impact of the hurricanes on pregnancy and birth outcomes, food and water insecurity, chronic disease risk, HIV care, and cancer care, spirituality-based coping, and resiliency and health among older adults.[2029]

The many factors discussed come together and result in disparities in health that is felt at the population level. Together, they cause substantive and measurable racial and ethnic differences in prevalence, severity, persistence, and progression of disease. Studies seeking to explain how this happens across diseases at the population level are complex and necessarily involve a multidisciplinary approach to investigation. The progress of each disease is different, as are the needs and contexts of each group of individuals.

The Immigrant Health Initiative—led by NIMHD with collaboration from NCI, NIAAA, NIDA, NIDCR, and NIEHS—seeks to address the etiology of health disparities and health advantages among immigrant populations. The complex immigration experience may result in limited English proficiency and low health literacy, both of which may contribute to barriers to accessing health care and effective patient-clinician communication. Furthermore, lack of health insurance, as well as use of traditional health practices, may act alone or in concert with many other factors throughout the life course to contribute to differences in health outcomes in immigrant sub-populations. This initiative supports multidisciplinary research on the underlying processes resulting from immigration that lead to health disparities among immigrant populations, including migrant workers, recent immigrants, and first-generation immigrants.[2030] Another component of the Immigrant Health Initiative aims to build an evidence base for effective interventions that address risk and resilience within immigrant populations. The complexity of the experience of immigration demands an approach that reflects current understanding of social, environmental, biological, and behavioral determinants of health across the life course. This type of approach has been shown to be effective in understanding challenges experienced by immigrant groups and is therefore more likely to be result in sustainable approaches to improving health outcomes.[2031]

The NIMHD Mechanisms of Disparities in Chronic Liver Diseases and Cancer program promotes research on understanding the complex causes of recent increases in liver disease and cancer disparities. Hepatocellular carcinoma is one of the few causes of cancer with increasing incidence and mortality in the U.S. It disproportionately affects disadvantaged populations of racial and ethnic minorities and individuals of low SES, who experience higher incidence and worse survival rates. The program will support research to understand the interplay of multiple risk factors—genetic, social, and environmental—as well as

[2029] https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-18-006.html.
[2030] https://www.nimhd.nih.gov/programs/extramural/investigator-initiated-research/immigrant-health-initiative.html.
[2031] https://www.nimhd.nih.gov/programs/extramural/investigator-initiated-research/immigrant-health-initiative_02.html.

metabolic causes of liver disease and cancer disparities in racial and ethnic minority and low SES populations. The role of health care access and quality of care for health disparity populations is also of interest, because it can result in late diagnosis, inadequate or limited access to treatment, and lower survival rates.[2032] Additional FY 2016–2018 updates on NIH efforts relating to cancer disparities are included in the Cancer subsection of this chapter.

The NIMHD Mechanisms of Disparities for HIV-Related Comorbidities in Health Disparity Populations Initiative supports research to understand the mechanisms and the effect of HIV-related comorbidities on the complexity of HIV/AIDS disease progression, quality of life, and overall health outcomes among individuals with HIV from health disparity populations. The overarching objectives of this initiative are to understand to what extent HIV-related comorbidities drive worse HIV-related health outcomes in health disparity populations. Studies leverage understanding of biological factors as part of multidisciplinary translational, population science, epidemiological, behavioral, or health services projects.[2033]

NIMHD also established five new Transdisciplinary Collaborative Centers (TCCs) for Health Disparities Research Focused on Precision Medicine in FY 2016. The goals of these TCCs are to advance understanding of the dynamic interplay between biological, behavioral, clinical, social and environmental health risk and protective factors experienced across the life course and to ensure greater inclusion of health disparity populations in research aimed at developing precision medicine interventions. Research conducted by the TCCs focuses on (1) identifying genetic and phenotypic markers representative of lifetime risks and outcomes for asthma, pre-term birth, cancer, and BMI in African American and Hispanic or Latino populations; (2) tracking health outcomes like type 2 diabetes and breast cancer in American Indian, Hispanic or Latino, and Chinese immigrant populations; (3) establishing the largest repository of pharmacogenomics information on African ancestry to facilitate genomic research and translational research; (4) examining minority men's health to determine the most effective ways to integrate, interpret, and apply biological, social, psychological, and clinical determinants of disease risks and outcomes into more precise medical strategies to prevent, diagnose, and treat chronic health conditions and diseases; and (5) identifying and testing culturally relevant and low-resource interventions to reduce the population burden of hypertension and type 2 diabetes and to inform clinical care delivery to individuals of African descent and Hispanic or Latino patients at high risk for hypertension and diabetes.[2034]

NIMHD launched the Collaborative Minority Health and Health Disparities Research Initiative in partnership with the Tribal Epidemiology Centers (TECs) of the Indian Health Service (IHS) and six NIH ICs and the Office of the NIH Director. The Initiative supports collaborative research between TECs and extramural investigators on topics related to minority health and health disparities among AI/AN populations, particularly in areas where there are significant gaps in data and knowledge. TECs can propose observational or intervention studies using data from TECs and collaborate with academic researchers, tribal governments, tribal organizations, clinicians, health care organizations, public health

[2032] https://www.nimhd.nih.gov/programs/extramural/investigator-initiated-research/liver-cancer.html.
[2033] https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-18-002.html.
[2034] https://www.nimhd.nih.gov/programs/extramural/research-centers/tcc/index.html.

organizations, school systems, faith-based organizations, or other relevant stakeholders. Partnerships will support community-responsive, scientifically rigorous projects with findings disseminated to local stakeholders, the IHS, and the scientific community. One TEC project focuses on evaluating the magnitude of motor vehicle injury disparity among Tribes in the Northwest region of the U.S. The project will report and map local motor vehicle injury, including injury severity and crash-related factors. Another project is examining the impact of the Navajo junk food tax in reducing obesity rates.[2035]

Addressing Health Disparities

A range of interventions has been designed and studied to address health disparities. To that end, NIH has also sought to coordinate and refine the research process.

In 2016 and 2017, THRO prepared reports detailing research accomplishments and activities in collaboration with NIMHD and all the ICOs that supported AI/AN research. The report was written based on individual NIH projects or center/collaborative grants, covering a range of research topics and accomplishments that supported the NIH mission research in behavioral and mental health, cancer, CVD, collaborative research, diabetes, elder health, environmental health, the genome, pediatric health, infectious diseases, obesity, renal disease, and substance-related disease.[2036,2037]

Among the accomplishments reported are studies examining interventions to address health outcomes within disparities populations. In 2016, about 3,600 sudden unexpected infant deaths (SUIDs) occurred in the U.S., among infants less than 1 year old, with no immediately obvious cause. According to CDC data from 2012 to 2015, AI/AN infants have the highest mortality rate from SUIDs (196.9 deaths per 100,000 live births), about twice the rate of non-Hispanic white infants (84.5 deaths per 100,000 live births). Healthy Native Babies Project (HNBP) is an extension of NIH's national Safe to Sleep® public education campaign that focuses specifically on the AI/AN community. NICHD's HNBP supports training and outreach to educate AI/AN families, community health leaders, and other caregivers about safe infant sleep practices.[2038]

The NIH American Indian and Alaska Native Health Communications and Information Work Group, led by NIAMS, partnered with IHS and the Administration for Community Living (ACL) to distribute an electronic newsletter called *Honoring Health: Resources for American Indians and Alaska Natives*. The purpose is to increase awareness of health information and resources available from NIH and other federal agencies. The newsletter is distributed three times a year to AI/AN intermediaries, specifically IHS Community Health Workers and ACL Title VI grantees working with Native elders. Each issue features a health topic and highlights resources, events, training, and grants and funding opportunities.[2039]

[2035] https://grants.nih.gov/grants/guide/pa-files/PAR-17-484.html.
[2036] https://dpcpsi.nih.gov/sites/default/files/NIH_FY_2016_AI_AN_Activities.pdf.
[2037] https://dpcpsi.nih.gov/sites/default/files/dpcpsi/document/NIH%20FY2017%20Annual%20Health%20Research%20Report%20-FINAL%2011-6-18_508.pdf.
[2038] https://www.nichd.nih.gov/sts/news/videos/healthynative/Pages/default.aspx.
[2039] https://www.niams.nih.gov/newsletters/aian-newsletter/2018.

Figure 117. The Healthy Native Babies Project is an adaptation of the national Safe to Sleep® campaign. Credit: NIH.

Two NIMHD TCCs for Health Disparities Research on Chronic Disease Prevention were established in FY 2016 with collaboration from a variety of ICOs, including NCI, NIA, NIAAA, NCCIH, NIDA, and ORWH. The Flint Center for Health Equity Solutions, based in Flint, Michigan, is serving as a regional focal point for organizing a broad cross-section of stakeholders with an interest in eliminating health disparities. Research projects include studying physical activity and healthy food interventions delivered in African American churches and a multi-tiered intervention program for men and women in recovery from substance misuse. The second new TCC is based in Washington state with partners in Alaska, Colorado, and Oklahoma and is examining disparities in hypertension, CVD, and stroke among American Indians, Alaska Natives, Native Hawaiians, and Pacific Islanders. Research projects are focused on harnessing technologies available where participants live, work, and obtain health care. These include electronic health records, text messaging, grocery shopping applications (apps), wearable physical activity monitors, and home blood pressure monitors.[2040]

In a collaboration with the Patient-Centered Outcomes Research Institute (PCORI), NHLBI is funding two clinical trials to reduce disparities in the treatment of hypertension. One trial will compare the effectiveness of clinic-based standard of care plus audit, feedback, and education versus an intervention that uses a collaborative care team, a CHW, and specialist consultation to deliver contextualized, appropriately stepped care for patients with hypertension. The second trial will compare two strategies designed to improve blood pressure control in primary care practices serving rural African Americans with

[2040] https://www.nimhd.nih.gov/programs/extramural/research-centers/tcc/index.html.

low SES in the Black Belt, part of the Stroke Belt in the southeastern U.S. Each of these trials will have about 2,000 patients, and both are to be completed in 2019.[2041–2043]

Different strategies have been examined, including those taking advantage of technology and new techniques. Results from a study funded by NCCIH showed yoga and physical therapy offer similar pain-relief and functional benefits to people with low SES who had chronic low-back pain. These improvements were greater than those observed from self-education. These findings suggest that a structured yoga program may be an alternative to physical therapy for people with chronic low-back pain, depending on individual preferences, availability, and cost.[2044,2045]

NIDCR established an Oral Health Disparities and Inequities Research Consortium to minimize inequities in access to care and improve the oral health of children. Current studies are focused on financial incentives to improve oral health behaviors, multilevel oral health interventions in primary care settings, text message–based interventions to reduce caries in children, and family-focused oral health education and support from community health workers.[2046–2050] NLM has also funded the creation of a smartphone app to help motivate and enable African American and Hispanic patients to assemble and use prevention-focused personal health libraries.[2051]

Along a similar vein, NIMHD-funded researchers sought to capture diagnosis of HIV among men who have sex with men (MSM) through testing both at home and at a medical facility. Investigators found that the detection of new infections was as effective using at-home HIV test kits as in-person data collection and HIV testing. Thus, using at-home HIV test kits in online HIV prevention research is not only feasible but may be particularly useful in engaging hard-to-reach MSM, such as those in rural areas.[2052]

Upstream from diagnosis, the NIMHD Behavioral Interventions to Prevent HIV in Diverse Adolescent Men Who Have Sex with Men Initiative sought to test behavioral HIV prevention interventions for diverse populations of adolescent MSM across each NIH-designated health disparity population. Three cooperative agreement awards were made in FY 2016. Each award includes innovative ways to engage diverse young MSM in online interventions to address the unique HIV risks faced by this vulnerable population, including gamification, chat rooms, and peer-led motivational interviewing.[2053]

[2041] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-021.html.
[2042] https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v%3Aproject=hsrProj&query=20162130.
[2043] https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v%3Aproject=hsrProj&query=20162135.
[2044] https://nccih.nih.gov/research/results/spotlight/yoga-low-back-pain.
[2045] Saper RB, et al. *Ann Intern Med* 2017;167(2):85-94. PMID: 28631003.
[2046] https://projectreporter.nih.gov/project_info_description.cfm?aid=9544146&icde=42317576.
[2047] https://projectreporter.nih.gov/project_info_description.cfm?aid=9544147&icde=43317192.
[2048] https://projectreporter.nih.gov/project_info_description.cfm?aid=9544164&icde=43317192.
[2049] https://projectreporter.nih.gov/project_info_description.cfm?aid=9544145&icde=43317192.
[2050] https://projectreporter.nih.gov/project_info_description.cfm?aid=9544163&icde=43317192.
[2051] https://projectreporter.nih.gov/project_info_description.cfm?projectnumber=1R01LM013039-01.
[2052] Hall EW, et al. *J Acquir Immune Defic Syndr* 2017;75(5):e142-e144. PMID: 28277488.
[2053] https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-15-012.html.

Policy has also been examined as an effective way to address disparities. All state Medicaid programs support application of fluoride varnish, a coating material that prevents caries, to children's teeth by primary care doctors. Researchers funded by NIDCR examined the national impact of these policies on children's oral health using data from the National Survey of Children's Health. Because these policies were adopted by individual states over 20 years, researchers were able to examine the association between the years since a state implemented a fluoride varnish policy and teeth quality, as well as compare children in states with fluoride varnish policies to those in states without. Fluoride varnish policies were associated with better oral health, and children in states that had these policies for 4 or more years had significantly greater odds of having very good or excellent teeth compared to those in states without.[2054]

In addition to studying interventions, NIH has identified specific areas where additional research should be conducted and provided data about what research is ongoing. An interactive AI/AN health research grant finder for FY 2014, 2015, and 2016 was developed, providing a digital image of the U.S., divided according to the 12 geographic areas served by IHS. Data from the FY 2016 report mentioned earlier in this report were made available on the site and link to specific projects on the NIH RePORTER site.[2055]

NICHD, along with nine other NIH ICOs, initiated a group of FOAs entitled The Health of SGM Populations. These announcements solicit basic, social, behavioral, clinical, and services research projects to increase scientific understanding of SGM health status.[2056] In collaboration with 13 other NIH ICOs, NICHD also initiated a group of FOAs entitled Research on the Health of Transgender and Gender Nonconforming Populations, which will support research projects on the health of TGNC people.[2057]

Given critical scientific gaps remaining in our understanding of the underlying biological mechanisms that contribute to differences in oral cancers, early childhood caries, dental caries, and periodontitis, NIDCR released an initiative to encourage studies aimed at understanding the biological factors that mediate the increased prevalence and severity of diseases and conditions in oral health disparities populations.[2058,2059]

While researchers may apply for grants under these new FOAs, those who already have a grant may also apply for administrative supplements to expand their research specifically to address health disparities.

One such effort is supported by ORWH for interdisciplinary research focused on the effect of sex and gender at the intersection of social determinants of health and disease—including, but not limited to, race and ethnicity, SES, education, health literacy, gender identity, and urban/rural residence. These administrative supplements are available for 1 year to active NIH grants supporting preclinical, clinical, or behavioral studies. The purpose of the supplement is to address health disparities among populations of

[2054] Kranz AM, et al. *Matern Child Health* 2019;23(1):100-108. PMID: 30032444.
[2055] https://dpcpsi.nih.gov/thro/tribal-area-information-fy-2016.
[2056] https://grants.nih.gov/grants/guide/pa-files/PA-18-037.html.
[2057] https://grants.nih.gov/grants/guide/pa-files/pa-18-729.html.
[2058] https://grants.nih.gov/grants/guide/pa-files/PA-18-874.html.
[2059] https://grants.nih.gov/grants/guide/pa-files/PAR-18-875.html.

women in the U.S. who are understudied, underrepresented, and underreported in biomedical research.[2060]

The SGM Administrative Supplement calls for research that will enrich scientific understanding of how sexual orientation, gender identity, and/or being born with DSD/intersex conditions relate to health and health risks, perceptions and expectations about health, health behaviors, and barriers and access to health-related services. Appropriate topics and studies for these supplements include, but are not limited to, addition of SGM individuals to a study that either originally excluded them or has not enrolled enough SGM participants to make any meaningful comparisons between groups.[2061–2063]

The research community has also been called upon to help set the research agenda for minority health and health disparities research. In April 2018, SGMRO hosted a 1.5-day workshop to identify research opportunities in SGM-related methods and measurement. The planning committee included both NIH staff and extramural researchers, who designed the workshop agenda and developed a schema to guide the discussions. The workshop focused on three areas: measurement of SGM status, measurement of core SGM health constructs, and sampling.[2064]

Furthermore, NIH has invested in developing and assessing approaches to ensure that research is relevant and of high quality. In particular, because disparities populations are by definition disadvantaged, this necessarily includes circumspect consideration of ethical concerns surrounding involvement in biomedical research.

In February 2017, THRO organized an NIH Informational/Consultation Session on Tribal Interests in Research Involving Human Participants. The session brought together participants from across the many NIH ICs to listen to tribal leaders, officers, and members share their perspectives or raise questions about protection of participants in biomedical research.[2065] Later in the same year, participants from NHGRI and THRO published an open commentary, providing guidance on interpreting regulations on protection of human participants specifically within the context of research conducted within AI/AN communities.[2066]

An understanding of both identity and heritage is also necessary to conduct effective research, particularly for addressing the needs of the AI/AN community. In recognition of Native American Heritage Month, THRO announced the Storytelling About Health and Wellness in American Indian and Alaska Native Communities Challenge. The goal of this Challenge was to develop a brief digital story (i.e., a video) that communicates how traditions and heritage promote health in AI/AN communities. The Challenge began in November 2016 and winners were announced in March 2017.[2067]

[2060] https://grants.nih.gov/grants/guide/pa-files/PA-18-676.html.
[2061] https://grants.nih.gov/grants/guide/pa-files/pa-15-329.html.
[2062] https://grants.nih.gov/grants/guide/pa-files/pa-17-098.html.
[2063] https://grants.nih.gov/grants/guide/pa-files/PA-18-713.html.
[2064] https://dpcpsi.nih.gov/sgmro/measurement.
[2065] https://dpcpsi.nih.gov/thro/consultationFeb2017.
[2066] Hull, et al. *The American Journal of Bioethics* 2017;17(7)60-62, PMID: 28661757.
[2067] https://dpcpsi.nih.gov/thro/storytellingchallenge.

NIH also recognizes that the investigators who conduct research bring with them a perspective that influences the research they produce. As such, NIH has sought to encourage diversity among individuals trained to conduct research and nurture an understanding of the challenges facing disparities populations across the biomedical workforce. To that end, SGMRO hosted a series of regional workshops in SGM health research to build capacity within the research community. The first workshop was held in conjunction with The Fenway Institute in Boston on May 12, 2018. The second was held in February 2019 at UCLA in conjunction with The Williams Institute.[2068] Other examples of how NIH is working to increase research workforce diversity are described in the "Research Workforce Recruitment, Training, and Retention" section of Chapter 1.

NICHD's IRP also continues to engage intersex patients and patients with DSDs and their families at the NIH CC–based fellowship training programs in pediatric endocrinology and medical genetics. NICHD's IRP researchers are actively involved in transnational efforts to advance SGM research and training, and they participate in a consortium of endocrine training programs that have related, active clinical programs.[2069]

The Native American Research Centers for Health (NARCH) program supports research and research training of AI/AN investigators. NARCH funds research projects prioritized by the tribal communities that address health issues disproportionately affecting the AI/AN communities, enhance health research partnerships, and reduce distrust of research by AI/AN communities. These research and training activities help develop a cadre of AI/AN scientists and health research professionals. In FY 2018, the NIGMS supported the NARCH program with $5.96 million and coordinated the effort of another 11 NIH ICs that together contributed an additional $3.8 million to the program. NARCH funded 17 grants, including 46 different projects in FY 2018, for research, student development, administrative purposes, faculty development, and capacity building.[2070]

The Research Centers in Minority Institutions (RCMI) is a research capacity–building, training, and mentoring program to advance scientific inquiry at institutions with a documented historical and current commitment to educating and serving underrepresented populations. The purpose of the RCMI program is to expand the national capacity for research in the health sciences by providing support to institutions that offer doctoral degrees in the health professions or in a health-related science, including clinical professional degrees. To be eligible to apply, institutions cannot receive more than $50 million per year on average in total NIH support within the 3 years prior to the time of application. The RCMI program was modified to align better with NIMHD's vision to advance the science of minority health and health disparities and to allow NIMHD staff to have more substantial programmatic involvement.[2071]

The NIMHD Specialized Centers of Excellence program conducts transdisciplinary, multilevel research and provides research opportunities for postdoctoral fellows, junior faculty, and other early-stage investigators. Centers are expected to have a unifying thematic focus with research activities that will

[2068] https://www.scgcorp.com/sgmroregional2018.
[2069] https://www.nichd.nih.gov/about/org/dir/osd/tp/peitp.
[2070] https://www.nigms.nih.gov/capacity-building/division-for-research-capacity-building/native-american-research-centers-for-health-(narch).
[2071] https://www.nimhd.nih.gov/programs/extramural/research-centers/rcmi/index.html.

embrace a multi-domain, multilevel perspective and are anticipated to have a direct and demonstrable impact on addressing minority health and health disparities in the thematic topic area. All center activities—including research projects, pilot projects, and community dissemination activities—are designed to contribute to this impact.[2072]

The Building Population Health Research Capacity in the U.S.-Affiliated Pacific Islands initiative aims to increase capacity to conduct ongoing population health research in the U.S.-Affiliated Pacific Islands, including American Samoa, Guam, and the Commonwealth of the Northern Mariana Islands, as well as three sovereign states that have a Compact of Free Association with the U.S.: the Federated States of Micronesia, the Republic of the Marshall Islands, and the Republic of Palau. In FY 2016, NIMHD awarded two cooperative agreements under this initiative, one to examine risk factors for cardiometabolic diseases in mother–child pairs in Guam and Pohnpei and another to examine colorectal cancer literacy and risk in American Samoan adults.[2073]

Going beyond the biomedical research community, the participation and engagement of disparities communities themselves is key to successfully understanding and addressing the challenge of improving health outcomes across communities.

The first HHS tri-operative division Consultation with Tribal Nations on the Opioid Crisis in Indian Country was held with NIH, IHS, and SAMHSA in Minnesota in May 2018.[2074,2075] As a result and in response to Tribal leader recommendations, multiple funding initiatives were created to help these communities heal and recover. An additional workshop, held in New Mexico in August 2018, which focused on tribal data sharing and genetic policy development, brought together community members, local legislators, and researchers to discuss the risks and benefits of participating in genetic research.[2076]

The NIH's Tribal Advisory Committee (TAC) In-Person Meeting is a biannual meeting that provides a forum for elected Tribal officials or their designated representatives and NIH officials to exchange views, share information, and seek advice concerning intergovernmental responsibilities related to the implementation and administration of NIH programs. The committee was established to help ensure that the Tribes and AI/AN people have meaningful and timely input in the development of NIH policies, programs, and priorities. The NIH TAC seeks to ensure that NIH policies or activities that affect AI/AN communities are brought to the attention of Tribal leaders.[2077]

Consultations were conducted between NIH and tribal leaders that foster respectful engagement and understanding on environmental and health research, because these impact tribal research capacity building, exposure to environmental agents, and health. Sustainable solutions for environmental and

[2072] https://www.nimhd.nih.gov/programs/extramural/research-centers/specialized-coe/index.html.
[2073] https://grants.nih.gov/grants/guide/rfa-files/rfa-md-15-011.html.
[2074] https://dpcpsi.nih.gov/thro/consultationMay2018.
[2075] https://dpcpsi.nih.gov/thro/nih-tribal-consultation-opioid-crisis-indian-country.
[2076] https://dpcpsi.nih.gov/sites/default/files/dpcpsi/document/Meeting%20Summary_Tribal%20Genetic%20Research%20and%20Data%20Sharing%20Policy%20Workshop_508.pdf.
[2077] https://dpcpsi.nih.gov/thro/tac.

human health concerns were also discussed during this consultation, held at the Phoenix Convention Center, Phoenix, Arizona, in October 2016.[2078]

A focused consultation was also held in 2017 by NIH with tribal Nations specifically to provide guidance and recommendations for the development of the NIH THRO Strategic Plan. The consultation sought to gather input on how NIH can improve all aspects of its interactions with tribal Nations and work together to identify the key topics that the THRO should prioritize for the next 5 years.[2079]

The 2018 National Native American Heritage month celebration at NIH featured a presentation from and discussion with Dr. Joseph Gone, clinical-community psychologist and Professor of Anthropology and of Global Health and Social Medicine at Harvard University. As the celebration's special guest, Dr. Gone shared his thoughts and discussed AI/AN therapeutic traditions and modern health treatments. This event was held in November 2018 on the NIH Bethesda campus.[2080]

From October 2017 to August 2018, NHLBI staff conducted listening sessions with representatives of several AI/AN communities involved in the Strong Heart Study. The purpose of the listening sessions was to enhance direct communication between NIH and the sovereign governments of the participating communities to guide and facilitate future research.

NIEHS has made a continued effort to highlight the importance of tribal ecological knowledge in conducting culturally relevant research with tribal Nations. Collaborative efforts have resulted in a set of recommendations for federally funded research focusing on including tribal community members in most facets of the research process.[2081,2082]

The results of such engagement show that scientists who engage communities in research and promote the integration of underserved populations strengthen the quality and adoption of research results. An example of this is found in the UCLA Clinical Translational Science Institute (CTSI) barbershop project. Black men are more likely to die from complications of high blood pressure than any other group in the U.S. The UCLA CTSI hub is supporting a study that pairs pharmacists with barbershops to offer high blood pressure care for customers. The results of this project show that this approach can dramatically lower blood pressure.[2083,2084]

Another example of community engagement is embodied in the Make Your Plan to Protect Your Sight Initiative, a new initiative from the National Eye Health Education Program, designed to raise awareness about eye health among African Americans. This initiative offers monthly resources to organizations so

[2078] https://dpcpsi.nih.gov/thro/consultationOct2016.
[2079] https://dpcpsi.nih.gov/thro/consultationJun2017.
[2080] https://dpcpsi.nih.gov/sites/default/files/pictures/2018_NAHM_save-the-date_final_508.pdf.
[2081] https://www.niehs.nih.gov/research/supported/translational/peph/webinars/tribal/index.cfm.
[2082] Finn S, et al. *Environ Health Perspect* 2017;125(8):085006. PMID: 28858824.
[2083] https://ncats.nih.gov/pubs/features/ctsa-barbershops.
[2084] Victor RG, et al. *N Engl J Med* 2018;378(14):1291-1301. PMID: 29527973.

they can promote healthy vision and help prevent vision loss and blindness in the communities they serve. Community resources include drop-in articles, fact sheets, and social media posts.[2085]

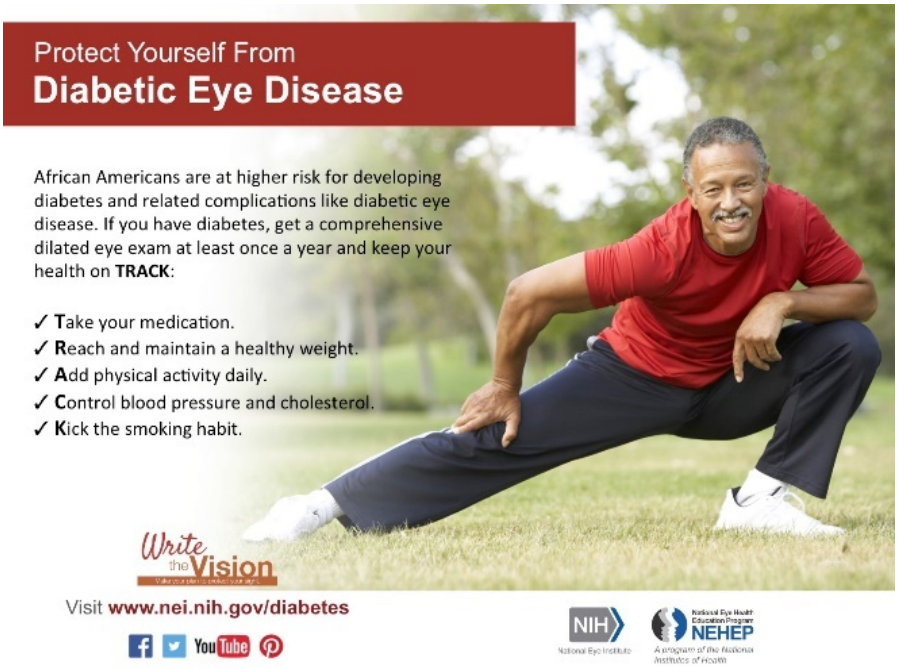

Figure 118. "Protect Yourself from Diabetic Eye Disease": Infographic. Credit: NIH.

Engagement with communities in this sense goes beyond speaking and interacting with the community and instead demonstrates the importance of having advocates and health professionals develop and provide access to culturally and linguistically appropriate health information. To assist with outreach efforts, NIAMS launched a Community Outreach website in FY 2017. The new site features a large collection of resources on bones, joints, muscles, and skin to help make community health activities a success. It contains health information—categorized by disease type, generation, and sex and gender—that community intermediaries can access for their audiences. It also features social media sharing tools, including a set of eye-catching graphics that can easily be shared with constituents to promote better health.[2086]

Ultimately the goal is to work quite closely with disparities communities—or to "transcreate." Transcreation: An Implementation Science Framework for Community-Engaged Behavioral Interventions to Reduce Health Disparities describes a framework for designing and delivering interventions in communities to reduce health disparities. The Transcreation Framework for Community-Engaged Behavioral Interventions to Reduce Health Disparities comprises seven steps: (1) Identify community infrastructure and engage partners; (2) specify theory; (3) identify multiple inputs for a new program; (4) design an intervention prototype; (5) design a study, methods, and measures for the community

[2085] https://nei.nih.gov/nehep/programs/writethevision.
[2086] https://www.niams.nih.gov/community-outreach-initiative.

setting; (6) build community capacity for delivery; and (7) deliver the transcreated intervention and evaluate implementation processes.[2087]

Emerging Technologies

Biomedical research is enabled and accelerated by the development of advanced technologies. As new knowledge is generated within a research topic, progress is often limited by the tools available. New tools need to be generated to overcome research bottlenecks in an ever-reinforcing cycle that drives scientific progress forward. NIH support in this area not only brings together different disciplines, ranging from applied physics to electrical engineering and cell biology, but also drives our understanding of health and disease and continues to lead to improvements in human health.

Summary of NIH Activities

The development of cutting-edge scientific techniques and technologies is supported across NIH and has transformed many research fields, putting the U.S. in a prime position to drive biomedical research forward. NIH funds and conducts research on innovative tools that facilitate biomedical research across the whole research continuum outlined in Chapter 2. These tools range from those needed for basic early-stage research (e.g., microscopy and cellular analysis tools) to technologies used in preclinical (e.g., tissue chips) and clinical research (e.g., imaging), as well as technologies that have real-world applications (e.g., point-of-care technologies); many recent examples are outlined in this section. NIGMS offered two new technology development FOAs to support concepts and prototypes that can be validated to work but are not yet ready to be used by the biomedical community to acquire new biomedical knowledge. One is for small innovative exploratory projects to evaluate the feasibility of concepts and ideas that have not yet been realized but have the potential to move to the development of prototypes, and the second is for focused technology development that has the likelihood of creating enabling biomedical technologies where working prototypes are created based on feasible concepts.[2088] So far, these funding opportunities have attracted novel proposals to build new microscopes and analytical technologies for understanding molecular structure and dynamics, as well as new molecular techniques to alter proteins and genes to reveal normal function and develop new molecular tools. Since the program began, the research supported by these grants has contributed to more than 50 patents with opportunities to advance the full range of biological research objectives of the Institute. In addition, NIBIB was established in 2000, with the focus of leading the development and accelerating the application of biomedical technologies.[2089]

NIH also organizes and funds meetings and symposia on technology development to bring scientists together to advance the field. NINR exemplified this approach by hosting a *Precision Health: Smart*

[2087] Nápoles AM, et al. *BMC Health Serv Res* 2018;18(1):710. PMID:30208873.
[2088] https://www.nigms.nih.gov/about/overview/BBCB/biomedicaltechnology/Pages/technologydevelopment.aspx#exploratory.
[2089] https://www.nibib.nih.gov/about-nibib/mission.

Technologies, Smart Health Symposium in 2018, which featured scientific panels and a poster session aimed at engaging graduate nursing students, nursing faculty, and clinicians interested in the clinical applications and clinical focus of smart health, smart technologies, digital health data, wearables and sensors, virtual or augmented reality, and molecular -omics data.[2090]

Illustrative of NIH's commitment to advancing biomedical research through the funding of new technologies, NIH funding for biotechnology was $6,433 million in FY 2016, $6,556 million in FY 2017, and 6,923 million in FY 2018; funding for bioengineering was $3,841 million in FY 2016, $4,106 million in FY 2017, and $4,592 million in FY 2018; and funding for biomedical imaging increased from $1,361 million in FY 2016 and $2,083 million in FY 2017 to $2,207 million in FY 2018.[2091] Several technology fields where recent notable advancements have been made are outlined in the following subsections, and some examples appear in other sections of Chapter 3.

Point-of-Care and Wearable Technologies, mHealth, and Telemedicine

Point-of-Care Technologies

Cutting-edge technologies are increasingly emerging as efficient and cost-effective ways to rapidly provide diagnostic and health status information on patients at the point of care. Intramural investigators at NIDCR and NIAID collaborated to create an economical, robust, and rapid point-of-care immunoassay technology that can rapidly and accurately measure antibodies to help diagnose infectious and autoimmune diseases in clinical settings in less than one minute per sample. Researchers have coupled the technology with a hand-held, battery-operated instrument for portable detection of different infectious and autoimmune diseases, including HIV, Epstein-Barr Virus, and Sjögren's syndrome.[2092] Similarly, NICHD researchers supported by an STTR grant are working to develop an electrochemical assay and validation of a point-of-care instrument for monitoring oxytocin in saliva. Oxytocin is a hormone that facilitates the birth process through induction of muscle contractions. Studies suggest correlations between exogenous administration of oxytocin during childbirth and various neurological disorders later in life of the offspring. Therefore, a point-of-care instrument would be a valuable tool for researchers and medical professionals to monitor peripheral levels of oxytocin in peripartum women and newborn infants.[2093]

In addition to improving diagnostic and health status information at the point of care, technologies are being developed by NIH-supported researchers that bring the care to patients to accelerate health care delivery, minimize office visits, and ease the challenges of attending appointments due to geographical, physical, or income constraints. NICHD's Contraceptive Clinical Trials Network (CCTN) was established in 1996 to support research on male and female contraception and to conduct clinical trials of new

[2090] https://www.ninr.nih.gov/newsandinformation/newsandnotes/smarthealth-video.
[2091] https://report.nih.gov/categorical_spending.aspx.
[2092] Burbelo PD, et al. *Sci Rep* 2017;7(1):3818. PIMD: 28630417.
[2093] https://projectreporter.nih.gov/project_info_description.cfm?aid=9131542&icde=43405727.

contraceptive drugs and devices. CCTN clinical field centers are selected for their capacity to conduct Phase I, II, and III trials of oral, vaginal, intrauterine, injectable, implantable, or topical contraceptive drugs and devices. In low-resource settings, women may face multiple barriers to obtaining effective contraception methods whose use is wholly within their control. Research supported through the CCTN led to the 2018 FDA approval of a soft, flexible vaginal contraceptive ring that offers reliable protection against unintended pregnancy for a year and that a woman can insert and remove by herself. The ring, known as the Nesterone®/Ethinyl Estradiol One-year Vaginal Contraceptive System, dispenses a hormone combination and does not require refrigeration, an important consideration in low-resource settings.[2094,2095]

The NIH Common Fund's New Innovator Awards support exceptionally creative early-career investigators who propose innovative, high-impact projects that are of high risk and high reward.[2096] In an exciting example of true innovation, stewardship, and making science fun, a New Innovator awardee garnered significant media attention for creating a low-cost, hand-powered centrifuge that can separate blood into individual components in one and a half minutes.[2097–2099] Based on the design of a child's toy and using only paper, twine, and plastic, the centrifuge costs 20 cents, is easily assembled, and is durable.[2100] The paperfuge can be used in the diagnosis of such diseases as malaria and African sleeping sickness and could help make scientific tools more accessible.

Wearable Sensors

Wearable sensors are devices that can be worn on the body and enable the monitoring of health conditions or status and can provide instantaneous important information, which can be used to tailor treatment or avoid potentially life-threatening situations. NIH-funded researchers have advanced the field in wearable sensors by exploiting stretchable and flexible platforms, developing devices that not only can sense pertinent health information but can also administer treatment, measure blood alcohol treatment, and detect allergens in foods.

NIBIB-funded researchers are literally breaking barriers using ultrasound waves emitted from a flexible patch to accurately measure central blood pressure and help detect cardiovascular problems earlier.[2101] Scientists have taken an innovative approach to coupling ultrasound with wearables to engineer their prototype. A silicone patch capable of emitting ultrasound waves up to a depth of about 1.5 inches can monitor blood pressure waveform by continuously recording the diameter of a pulsating blood vessel.[2102]

[2094] https://www.nichd.nih.gov/research/supported/cctn.
[2095] Stifani BM, et al. *Contraception* 2018;97(5):415-21. PMID: 29269252.
[2096] https://commonfund.nih.gov/newinnovator.
[2097] https://www.npr.org/sections/health-shots/2017/01/10/508415046/childrens-whirligig-toy-inspires-a-low-cost-laboratory-test.
[2098] https://www.theatlantic.com/science/archive/2017/01/button-spinner-health-care/512549/.
[2099] https://www.cnn.com/2017/01/16/health/paperfuge-whirligig-disease-study/.
[2100] https://www.nature.com/articles/s41551-016-0009.pdf.
[2101] https://www.nibib.nih.gov/news-events/newsroom/wearable-ultrasound-patch-penetrates-skin-measure-blood-pressure.
[2102] Wang C, et al. *Nat Biomed Eng* 2018;2(9):687-95. PMID: 30906648.

Customized software translates the recorded measurements into a blood pressure waveform to show changes in blood pressure. The peaks and valleys of a waveform represent heart activity, which is used to indicate cardiovascular problems, such as hypertension, heart disease, and valve dysfunctions.

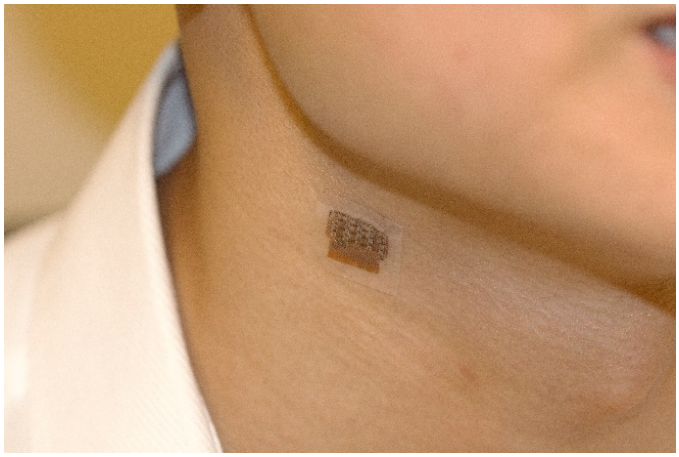

Figure 119. Small, wearable patch measures central blood pressure in the carotid artery. Credit: Adapted from Wang et al. Nature Biomedical Engineering.

In an example of using wearable sensors, NIAMS-, NIBIB-, and NHLBI-funded researchers collaborated on a smart bandage that offered real-time wound monitoring and tailored treatment delivery.[2103] Chronic wounds are a major health concern and affect the lives of more than 25 million people in the U.S. Wounds are susceptible to infection and are the leading cause of nontraumatic limb amputations worldwide. Wound healing can be enhanced by administration of therapies at the right time, which requires real-time monitoring of the wound environment with on-demand drug delivery in a closed-loop manner. The smart and automated flexible wound dressing with temperature and pH sensors integrated onto flexible bandages monitors wound status in real time to address this unmet medical need. Moreover, a stimuli-responsive drug-releasing system comprising a hydrogel loaded with thermo-responsive drug carriers and an electronically controlled flexible heater is also integrated into the wound dressing to release the drugs on demand. The dressing is equipped with a microcontroller to process the data measured by the sensors and to program the drug release protocol for individualized treatment. This flexible smart wound dressing has the potential to significantly impact the treatment of chronic wounds.

[2103] https://directorsblog.nih.gov/2018/07/26/building-a-smarter-bandage/.

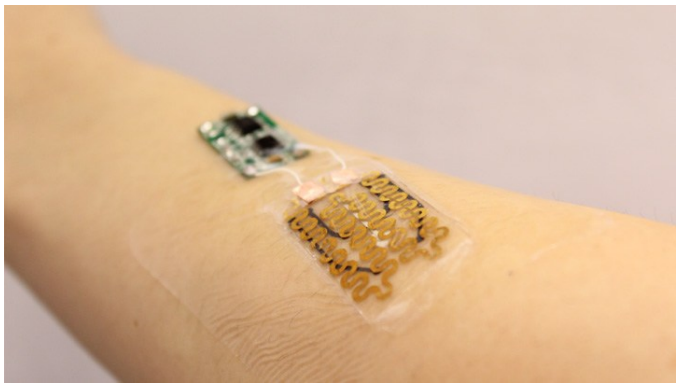

Figure 120. A prototype of a smart bandage equipped with temperature and pH sensors (center foreground) printed directly onto the surface of a thin, flexible medical tape. You also see the "brains" of the operation: a microprocessor (upper background). When the sensors prompt the microprocessor, it heats up a hydrogel-heating element in the bandage, releasing drugs or other healing substances on demand. It can also wirelessly transmit messages directly to a smartphone to keep patients and doctors updated. Credit: Tufts University, Medford, MA.

Approximately 88,000 people in the U.S. die from alcohol-related causes, including driving fatalities, which accounted for nearly 10,000 deaths in 2014.[2104] NIBIB-funded researchers designed a convenient method for individuals to monitor their alcohol intake, which could help reduce unsafe drinking that leads to vehicle crashes, violence, and the degeneration of the health of heavy drinkers.[2105,2106] This biosensor patch, which resembles a temporary tattoo, is embedded with several flexible wireless components. One component releases a chemical that stimulates perspiration on the skin below the patch. Another component senses changes in the electrical current flowing through the generated sweat, which measures alcohol levels and sends them to the user's cell phone.

NIAAA also issued a Wearable Alcohol Biosensor Challenge to stimulate the design of a discreet, noninvasive wearable device capable of measuring blood alcohol levels in near real time. In FY 2016, NIAAA awarded a $200,000 challenge prize to BACtrack, a company known nationally for designing and selling portable breath alcohol testers for consumer and professional use.[2107] Their winning prototype—the BACtrack Skyn—is a device that is worn on the wrist and offers continuous, discreet, noninvasive blood alcohol content monitoring by detecting alcohol released through the skin in sweat or vapor.[2108]

NCI, NIBIB, and NHLBI researchers developed a food allergy lab that fits on a keychain, which is not a wearable sensor per se but is generally kept close at hand. More than 50 million Americans have food allergies, and often just trace amounts of allergens can trigger life-threatening reactions. This $40 device fits on a key chain and can accurately test for such allergens as gluten or nuts in a restaurant meal in less

[2104] National Center for Statistics and Analysis. 2014 Crash Data Key Findings (Traffic Safety Facts Crash Stats. Report No. DOT HS 812 219). Washington, DC: National Highway Traffic Safety Administration. 2015. Available at: https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812219.
[2105] https://www.nibib.nih.gov/news-events/newsroom/wearable-tattoo-sends-alcohol-levels-your-cell-phone.
[2106] https://pubs.acs.org/doi/abs/10.1021/acssensors.6b00356.
[2107] https://www.niaaa.nih.gov/news-events/news-releases/niaaa-selects-winners-its-wearable-alcohol-biosensor-challenge.
[2108] https://www.bactrack.com/pages/bactrack-skyn-wearable-alcohol-monitor.

than 10 minutes.[2109,2110] This is an illustration of a case where researchers have taken the technologies they have developed for other medical problems, such as early cancer detection from blood samples, and applied them to solving the daily, potentially life-threatening difficulties in people with food allergies—a highly significant public health problem that incurs $25 billion in annual costs in the U.S. alone. The device consists of three components. A small plastic test tube is used to dissolve a small sample of the food being tested and to add the magnetic beads that capture the food allergen of interest, such as gluten. A bit of that solution is then dropped onto electrode strips on a small module, which is then inserted into the electronic keychain reader. The keychain reader has a small display that indicates whether the allergen is present, and if so, in what concentration. Testing showed that measurements of the allergen concentration are extremely accurate. In addition to contributing to food safety at the individual and community levels in the U.S., the inventors point out that the device would be valuable for travelers in countries where there are no specific requirements for food labels. Another use of the system would be to trace the source of food contamination with bacteria such as *E. coli* or Salmonella to a specific food-processing site by testing DNA in the samples to potentially identify and contain an outbreak more quickly.

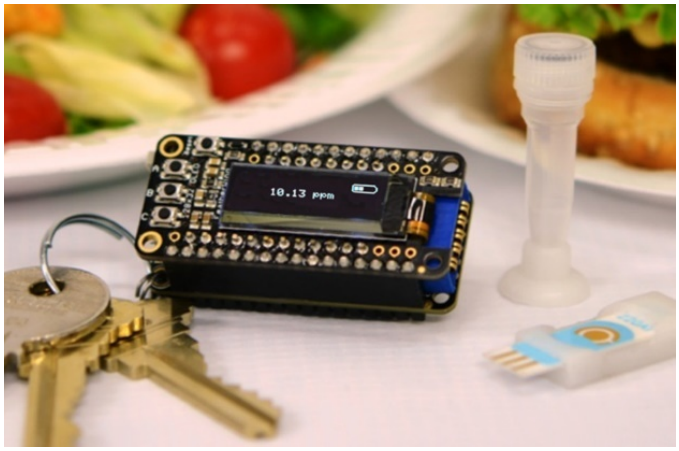

Figure 114. The iEAT system for onsite antigen detection consists of a pocket-size detector, an electrode chip, and a disposable kit for allergen extraction. The detector connects with a smartphone for system control and data upload to a cloud server. Credit: Lin, et al. *ACS Nano*, Aug. 2017.

mHealth and Telemedicine

mHealth uses mobile and wireless devices (cellphones, tablets, etc.) to improve health outcomes, health care services, and health research, whereas telemedicine involves the remote diagnosis and treatment of patients by means of telecommunications technology. One aspect of mHealth is the emerging field of telepresence. Every year, large numbers of students are not able to attend school because of illness. Extended absence from the classroom has negative and overlapping educational and social consequences because students may fall behind in instruction, feel isolated from their peers, and experience loneliness and depression. Telepresence robots may provide a way for chronically ill students to attend school virtually, participate in classes, ask questions and contribute to discussions, and remain connected to their

[2109] https://www.nibib.nih.gov/news-events/newsroom/food-allergy-lab-fits-your-keychain.
[2110] Lin H, et al. *ACS Nano* 2017;11(10):10062-69. PMID: 28792732.

classmates and teachers.[2111] The robots will also help children who are being treated for cancer or are undergoing surgery to keep up with their classmates while recovering. NCATS-funded research enabled an early-stage investigator to assemble a multidisciplinary team of technology and child development experts to examine the use of telepresence robots by home-bound children.[2112] Their findings will help to advance the emerging field of telepresence, in which virtual inclusion and engagement could potentially have an impact on child health and might have far-reaching implications for society.

According to epidemiological findings, 75,000 children die annually worldwide in pedestrian crashes. A study funded by FIC and OBSSR evaluated the use of classroom-based training in a smartphone-based virtual reality (VR) pedestrian environment.[2113] The study concluded that pedestrian safety training via smartphone-based VR provides children with the repeated practice sessions needed to learn the complex skills required to cross streets safely and helps them improve self-efficacy to cross streets. Children who engaged in the VR for 12 days in their classrooms honed complex cognitive-perceptual skills required to engage safely in traffic. Given rapid motorization and global smartphone penetration, smartphone-based VR could supplement existing policy and prevention efforts to improve global child pedestrian safety.

Several other examples of NIH-supported research involving the development of applications (apps) to benefit health are described. NIBIB researchers developed an app called Understanding Medical Scans, which is designed to help patients learn what to expect during a medical scan and how scans can help with both diagnosis and treatment.[2114] The app uses question-based navigation, images, and videos and makes medical imaging information easily available anywhere. It was designed to be understood by the layperson, to give patients basic information about what they are going to experience, and to help them ask more informed questions of their technologists. In 2018, NCCIH created the HerbList app,[2115] which provides research-based information about the safety and efficacy of select herbal products. This app serves as a resource for on-the-go facts about herbs and for learning and making informed health decisions. Patients and providers may also find the app to be helpful when discussing herbal products that a patient may be using or considering. The app pulls from the existing Herbs at a Glance series content on NCCIH's website.[2116] Included are 52 herbs and botanicals, with such information as their common names, what the science says, potential side effects and cautions, resources for more information on safety, and the potential for herb-drug interactions.

An NIEHS-funded research to action project will test the effectiveness of an interactive, culturally tailored mobile app called Gigiigooinaan, which means *Our Fish*.[2117] The app, focusing on Native American tribal communities living in and around the Great Lakes, will deliver personalized consumption advice on fish species commonly consumed by the tribal communities. Ongoing concern about the presence of

[2111] https://escholarship.org/uc/item/9zm4h7nf.
[2112] https://ncats.nih.gov/pubs/features/uc-irvine-robotics.
[2113] Schwebel DC, et al. *J Pediatr Psychol* 2018;43(5):473-84.
[2114] https://www.nibib.nih.gov/Understanding-Medical-Scans-App.
[2115] https://nccih.nih.gov/Health/HerbListApp.
[2116] https://nccih.nih.gov/health/herbsataglance.htm.
[2117] https://www.niehs.nih.gov/research/supported/translational/peph/prog/rta/cfg/mcw/index.cfm.

pollutants in the Great Lakes called persistent bioaccumulative toxics, which accumulate in fish, has led to numerous fish consumption advisories. Fish are an important part of the Anishinaabe diet and culture. Promoting environmental health in these tribal communities is critical, as is communicating the benefits of fish without increasing the risks of exposure to these bioaccumulative toxics.

Computational Technologies

NIH invests heavily in numerous cutting-edge computational technologies, such as computer-aided tools, machine learning, and software programs that streamline medical procedures and diagnoses, reduce costs, and help save lives. NLM's IRP has a strong focus on development and application of machine learning to improve the diagnosis and treatment of a wide range of diseases, often in collaboration with other NIH ICs. For example, NLM researchers worked with NCI's Division of Cancer Epidemiology and Genetics, Clinical Genetics Branch, to develop machine-learning algorithms for predicting cervical cancer using colposcopic, histology, and cytology images.[2118–2120] The deep learning models aid in interpreting cervical images to detect the presence of HPV infection (a cause of cervical cancer), improve classification of the disease, and assist in early treatment in low-resource areas.[2121,2122] NLM collected data from Boundary Marking Tool for the Cervical Biopsy Study at five sites in Costa Rica, Netherlands, Nigeria, Spain, and the U.S.. NCI and the American Society for Colposcopy and Cervical Pathology have used NLM's Teaching Tool to help train medical students and practitioners to detect cervical cancer.

Every year, thousands of people undergo orthognathic surgery, a procedure to correct jaw deformities, but many proven problems have been associated with traditional surgical planning methods for this surgery. To address these problems, a group of NIDCR-supported researchers developed a computer-aided surgical simulation planning tool called the AnatomicAligner and a streamlined protocol that allow clinicians to plan an entire jaw surgery using a single software system.[2123] Because of the complex structure of the jaw, this surgery requires extensive presurgical planning, including intricate and time-consuming manual mapping of anatomy. This tool will speed planning and may improve accuracy and outcomes of orthognathic surgery.

Next-generation sequencing (NGS) is transforming the field of genomics, playing a central role in the movement toward personalized medicine.[2124] The inherent personalized nature of selecting the best blood product for each patient, along with the breadth of genomic information potentially relevant for transfusion therapy (e.g., red blood cells [RBC], platelets [PLT], neutrophil antigens, and the human leukocyte antigen system) and the documented clinical value, make transfusion medicine an ideal field for the use of NGS data. Researchers at the NIH CC led the development of a novel computer software

[2118] https://lhncbc.nlm.nih.gov/project/imaging-tools-cancer-research.
[2119] Sornapudi S, et al. *J Pathol Inform* 2018;9(5). PMID: 29619277.
[2120] Guo P, et al. *J Pathol Inform* 2016;7(51). PMID: 28163974.
[2121] Xu T, et al. *Pattern Recognit* 2017;63:468-75. PMID: 28603299.
[2122] Hu L, et al. *J Natl Cancer Inst* 2019. PMID: 30629194.
[2123] Yuan P, et al. *Int J Comput Assis Radiol Surg* 2017;12(12):2129-43. PMID: 28432489.
[2124] Montemayor-Garcia C, et al. *Transfusion* 2018;58(2)277-9. PMID 29411394.

program called RyLAN (Red cell and Leukocyte Antigen), which is an innovative computational tool that translates NGS data into an extended RBC, PLT, and neutrophil antigen phenotype, which can be used to administer precise transfusion support throughout the lifetime of a patient. Through the use of RyLAN software and in collaboration with NHGRI and NHLBI, NGS was shown to be more precise than the FDA-approved serology and genetic blood typing methods currently used for patient support in the CC and nationally. This work has already resulted in the discovery of two novel blood group genomic variants that have important clinical implications.[2125]

Figure 115. DNA Double Helix with Data. Credit: Jonathan Bailey, NHGRI.

Imaging

NIH-supported researchers are developing cutting-edge imaging technologies to enhance the monitoring of patient's health status, improve the accuracy of medical procedures, and provide insight into basic cellular function.

Chronic skin wounds, such as diabetic foot ulcers and pressure wounds, affect more than 6 million people in the U.S., with the cost of treatments mounting to $25 billion each year. NIBIB and NIA-funded researchers demonstrated the novel use of a noninvasive imaging technique to monitor wound healing in live animals.[2126,2127] The scientists measured metabolic changes that occur during healing at the wound's surface using a technique called autofluorescence imaging. In the future, doctors could use the images to noninvasively diagnose the type of chronic wound and determine the best treatment strategy.

Another image-based technological development by an NIBIB SBIR grantee is a pocket-sized imaging device to aid doctors in the accuracy of epidural needle placement, which has the potential to reduce complications and improve the overall health care experience of the patient.[2128] The

[2125] Montemayor-Garcia C, et al. *Transfusion* 2018;58(11)2693-704. PMID 30312480.
[2126] https://www.nibib.nih.gov/news-events/newsroom/nibib-funded-researchers-use-non-invasive-imaging-technique-diagnose-monitor-chronic-wounds.
[2127] Jones JD, et al. *Commun Biol* 2018;1:198. PMID: 30480099.
[2128] https://www.nibib.nih.gov/news-events/newsroom/pocket-sized-imaging-device-improves-accuracy-epidural-placement.

novel ultrasound system incorporates hardware and software, including a computer-aided detection algorithm to enhance bone discernment—which typically is poor with ultrasound—to navigate the lumbar anatomy. The project also received a supplement for entrepreneurship development and has been cleared by the FDA. Scientists in NIBIB's IRP combined two different microscope technologies to create sharper images of rapidly moving processes inside a cell and achieved rapid, high-contrast super-resolution imaging.[2129] The microscopy laboratory now also has an Advanced Imaging and Microscopy Resource that is a trans-NIH shared resource that houses, operates, and disseminates optical imaging systems developed at NIH.[2130]

NIBIB- and NINDS-funded researchers developed a metal-free MRI contrast agent using nanotechnology to create an innovative system for safe and effective contrast agent delivery. Metal-free MRI agents could overcome the established toxicity associated with metal-based agents in some patient populations and enable new modes of functional MRI in vivo.[2131,2132]

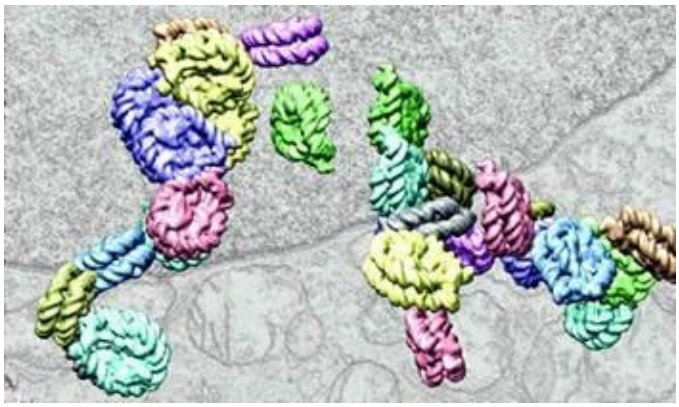

Figure 116. Computer-enhanced electron micrograph image of interacting chromatin chains of 5–24 nanometers in the cell nucleus. Credit: Clodagh C. O'Shea, Salk Institute, La Jolla, CA.

Researchers funded by NCI, NIBIB, NIGMS, and the NIH Common Fund developed a new electron microscopy–based technique called ChromEMT, which enables the 3-D structure and packing of DNA to be visualized inside the cell nucleus of intact cells. This technological advance overturned the long-standing textbook model of DNA folding and suggests more complex gene interactions and regulation. ChromEMT reveals how these complex biological structures are able to perform the myriad intricate and elaborate functions of the human body.[2133,2134]

NIH Common Fund, NHGRI, NIBIB, NIDA, NIMH, and NINDS funded researchers who are developing a new technique that makes it possible for conventional microscopes to produce super-high-resolution images

[2129] Guo M, et al. *Nat Methods* 2018;15(6):425-28. PMID:29735999.
[2130] https://www.nibib.nih.gov/labs-at-nibib/advanced-imaging-and-microscopy-aim-resource.
[2131] https://www.nibib.nih.gov/news-events/newsroom/nih-funded-researchers-develop-metal-free-mri-contrast-agent.
[2132] Nguyen HV, et al. *ACS Cent Sci* 2017;3(7):800-11. PMID: 28776023.
[2133] https://www.nibib.nih.gov/news-events/newsroom/new-imaging-technique-overturns-longstanding-textbook-model-dna-folding.
[2134] Ou HD, et al. Science 2017;357(6349). PMID: 28751582.

of brain cells by harnessing the highly absorbent properties of sodium polyacrylate, a polymer commonly used in diapers.[2135,2136] The process, initially developed in 2015,[2137] involves removing the molecules that make tissue rigid and opaque while retaining fluorescently labeled proteins of interest, thus allowing the tissue to expand evenly in three dimensions. The final product is a neural landscape with greatly enlarged cell structures that also appear transparent, making them perfect for microscopy. Expansion microscopy can provide jaw-dropping views of a wide range of biological systems and can be used to scan whole-brain structures and show entire neural networks in 3-D. In 2017, researchers improved on the technique to allow up to 20X expansion, which opened the door to visualizing incredibly tiny structures.[2138]

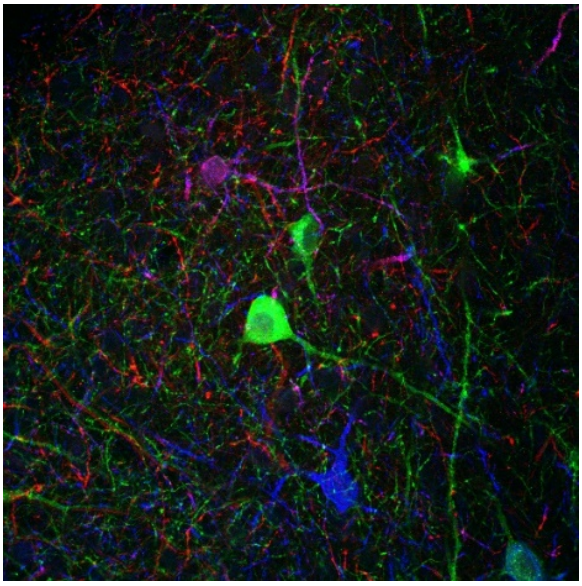

Figure 117. Vibratome slice from PVCre;Brainbow mouse that has been expanded about fourfold using protein retention expansion microscopy, taken with a 10x lens. Credit: Tim Petros, NICHD.

NIH supports the development of a variety of innovative and cutting-edge imaging technologies to achieve visualization in living human eyes not previously possible with existing technologies. Traumatic brain injuries and neurodegenerative diseases can alter the shape of photoreceptors, the light-sensitive cells of the retina. With the advent of adaptive optics, a game-changing technology that permits eye doctors to overcome bent light waves and distortions that normally interfere with imaging, researchers and clinicians now have the ability to image these individual cells in living patients in real time to diagnose disease and track anatomical changes in the retina. Unfortunately, adaptive optics-scanning laser ophthalmoscope (AOSLO) equipment is prohibitively large and expensive for most clinics. These barriers have so far prevented AOSLO from being widely used in the ophthalmology community. One group of NEI-funded researchers, however, has developed a hand-held AOSLO device capable of overcoming some of these

[2135] https://projectreporter.nih.gov/project_info_description.cfm?aid=9490296&icde=45000749&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=.
[2136] https://directorsblog.nih.gov/2019/04/11/an-indisposable-idea-from-a-disposable-diaper/.
[2137] https://directorsblog.nih.gov/2015/03/26/diaper-compound-brings-change-to-cell-microscopy/.
[2138] https://directorsblog.nih.gov/2019/02/07/mammalian-brain-like-youve-never-seen-it-before/.

barriers.[2139] The probe will benefit pediatric research by improving the understanding of retinal development, maldevelopment, and early onset of disease during human growth.

NEI intramural researchers have demonstrated a technique for visualizing RPE cells in the eyes of living human subjects, using a clinically safe intravenous dye called indocyanine green.[2140] In combination with adaptive optics, a game-changing technology permitting eye doctors to examine living cells during a patient's eye exam using a microscope, the community can now examine living cells in unprecedented detail without worrying about bent light waves or distortions marring the image.[2141] Many human diseases, such as age-related macular degeneration and many inherited retinal degenerations, result from diseased RPE. This technique provides a powerful new way to observe RPE longitudinally in patients at the single-cell level, which may be useful in monitoring the progress of potential therapeutics in a shorter time scale than is currently possible.

3-D Printing

More than 100,000 men, women, and children are on the national transplant waiting list in the U.S. alone, and 20 people die each day waiting for a transplant.[2142] 3-D printing technologies are garnering considerable excitement and the hope that these technologies may one day be able to serve as fully functional replacement organs originating from an individual's own cells and may perhaps ultimately serve as a supply of organs perfectly matched for transplantation.

NIBIB- and NHLBI-funded bioengineers developed a 3-D printer that creates a model of a patient's prostate that mimics the real organ—in terms of shape, size, and texture—and adds tactile feedback for surgeons to aid in surgery planning and rehearsal, which will help avoid medical errors and limit damage to surrounding nerves and healthy tissues. Although anatomically correct, 3-D-printed organs are typically made of hard plastic and cannot be cut or sutured. This new 3-D printer results in an anatomically accurate organ model, with the same elasticity and softness as the actual organ. The project shows how successfully mechanical engineers and medical doctors can collaborate to develop novel and promising technologies for medical treatment.[2143]

[2139] LaRocca F, et al. *Nat Photonics* 2016;10:580-84. PMID: 29479373.
[2140] Tam J, et al. *Invest Ophthalmol Vis Sci* 2016;57(10):4376-84. PMID: 27564519.
[2141] Jung H, et al. *Commun Biol* 2018;1:189. PMID: 3046310.
[2142] https://www.organdonor.gov/statistics-stories/statistics.html.
[2143] Qiu K, et al. *Adv Mater Technol* 2018;3(3). PMID: 29608202.

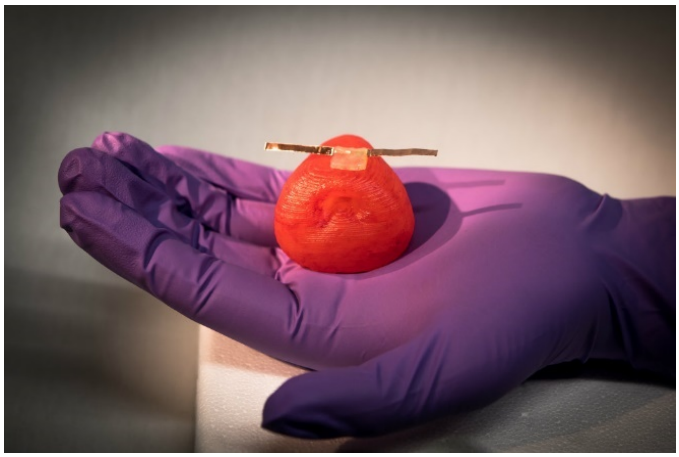

Figure 125. 3-D-printed model of a patient-specific prostate has the texture and elasticity of an actual prostate. The gold foil electrodes on top form contacts to the 3-D-printed sensor, which provides tactile feedback during surgical rehearsal. Credit: M. McAlpine, University of Minnesota.

In FY 2016, NICHD issued a FOA for the use of 3-D printing to create implantable devices to encourage applications for grant awards to utilize 3-D printing technologies to develop implantable devices and biodegradable scaffolds for long-term use that will adapt to the needs of growing children.[2144] Some examples of projects funded through this FOA include 3-D printing of multifunctional adaptive nerve conduits, personalized devices for craniomaxillofacial defects, tracheas (windpipes) for pediatric patients, and patient-specific vascular grafts.

Tissue Chips

Approximately 30 percent of promising medications have failed in human clinical trials because they are found to be toxic despite promising preclinical studies in animal models. About 60 percent of candidate drugs fail because of a lack of efficacy. NCATS, through its Tissue Chip for Drug Screening program and in coordination with other ICs and the FDA, addresses this problem by supporting 3-D platforms engineered to support living human tissues and cells called tissue chips or organs-on-chips.[2145] Tissue chip devices are designed as accurate models of the structure and function of human organs, such as the lungs, liver, and heart. Once developed and integrated, researchers can use these models to predict whether a candidate drug, vaccine, or biologic agent is safe or toxic in humans in a faster and more effective way than current methods. The goal of the program is to accelerate the translation of basic discoveries into the clinic. Researchers can use these models to test the safety and toxicity of candidate drugs in human tissue chips more rapidly. Funded through the Cures Acceleration Network, the Tissue Chip Testing Centers (TCTC) provide the means for scientists to test and validate tissue chip platforms independently; to ensure wide-ranging availability of tissue chip technology, particularly for regulatory agencies and pharmaceutical companies; and to promote the adoption of this technology by the broad research community.[2146]

[2144] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-17-002.html.
[2145] https://ncats.nih.gov/tissuechip/about.
[2146] https://ncats.nih.gov/tissuechip/projects/centers.

Three awards were funded in 2016, and in 2018, NCATS provided support to the TCTCs to advance the wider adoption of tissue chip technologies by the pharmaceutical and biotechnology industries, as well as regulatory agencies, and to transition this technology into commercialization. In FY 2017 and 2018, NCATS and partner ICs funded multiple institutions to further develop tissue chip models of human disease that mimic the pathology in major human organs and tissues.[2147,2148] The goals are to (1) support studies to develop in vitro disease models using primary tissue or iPSC-derived patient cell sources on tissue/organ chip platforms, (2) determine disease relevance of these models by preliminary testing of key experimental features, and (3) test the effectiveness of candidate drugs. This innovative technology encompasses expertise from disease experts and those from such fields as bioengineering, stem cell technology, organ physiology, pharmacology, toxicology, pathology, and regulatory science.

NCATS also partnered with the International Space Station U.S. National Laboratory (ISS National Lab) to collaborate on refining tissue chip technology for biomedical research use on the Space Station.[2149–2151] Translational research at the ISS National Lab provides unprecedented opportunities to study the effects of a microgravity environment on the human body because it is now widely known that symptoms of accelerated aging occur after prolonged exposure to microgravity (diminished or close to zero gravity compared with Earth). Health concerns that resemble aging—such as muscle deterioration, osteoporosis (bone loss), reduced cardiopulmonary function, and immune deficiency—have been documented in space, and researchers also have observed that these conditions are reversible when astronauts return to Earth. Tissue chip applications at the ISS National Lab enable studies of organs at the cell and tissue levels under reduced gravity, contribute to understanding the process of aging, could reveal molecular targets that can slow that process, and create opportunities to accelerate the development of translational technologies for earthly applications.

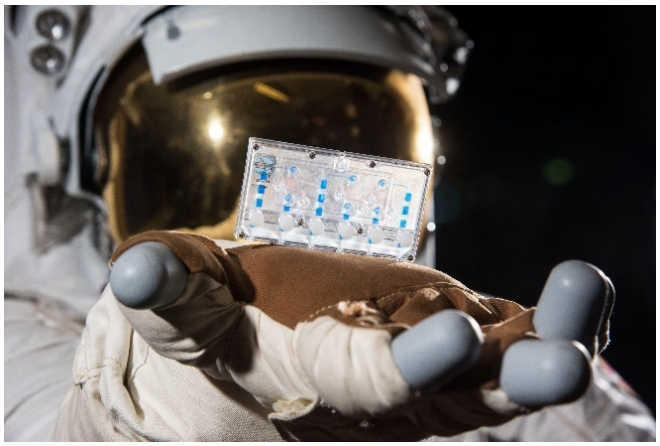

Figure 126. A NASA spacesuit is shown with a kidney tissue chip in hand. Credit: NASA.

[2147] https://ncats.nih.gov/tissuechip/projects/modeling.
[2148] https://www.nih.gov/news-events/news-releases/nih-awards-15-million-support-development-3-d-human-tissue-models.
[2149] https://ncats.nih.gov/tissuechip/projects/space.
[2150] https://www.nih.gov/news-events/news-releases/nih-funded-tissue-chips-rocket-international-space-station.
[2151] https://directorsblog.nih.gov/2018/12/04/blast-off-sending-human-tissue-chips-into-space/.

Cellular Function

Cellular functions include such basic life processes as protein and fat synthesis, cell division and replication, respiration, metabolism, and ion transport. These functions provide structural support for tissues, protecting the body against disease or injury, and serve as selective barriers to the passage of various materials into and out of the cell. NIH research in cellular function encompasses mapping and tracking individual cell types to tissues, characterizing how somatic cells can reprogram iPSCs, and insightful studies of DNA and RNA functions.

In 2018, the NIH Common Fund—along with NHLBI, NIBIB, and NIDDK—funded the first awards for the Human BioMolecular Atlas Program (HuBMAP) to develop an open, global framework to map the human body at the level of individual cells.[2152,2153] Leveraging recent advances in single-cell analysis technologies, HuBMAP researchers will generate foundational 3-D tissue maps; establish an open data platform to integrate, visualize, and model multiple types of data; accelerate the development of next-generation tools and technologies for tissue mapping; and collaborate with other organizations to build the framework for mapping the human body. The adult human body is composed of tens of trillions of cells carefully organized in tissues to carry out the daily processes that keep the body alive and healthy. The organization, specialization, and cooperation of different cells within each normal tissue have a profound impact on tissue growth, function, and aging. These factors can also indicate the emergence of disease. For example, immune cells reside in normal tissues as part of their regular surveillance duties. The ability to detect subtle changes in the activity of individual immune cells and in their interactions with other cells within tissues would help signal the emergence of disease before symptoms are clinically detectable.

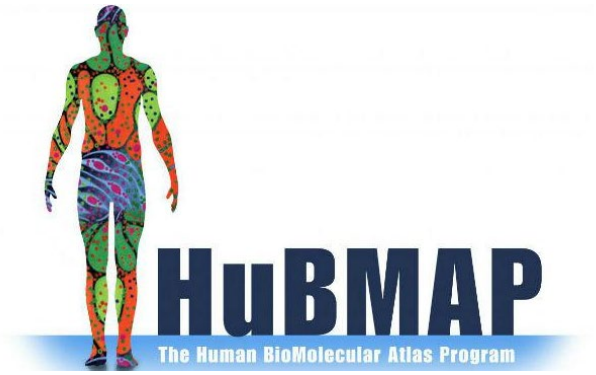

Figure 127. The goal of the HuBMAP is to develop an open and global platform to map healthy cells in the human body. Credit: NIH.

The Single Cell Analysis program, formerly supported by the NIH Common Fund in collaboration with NIBIB and NIMH, aims to accelerate the discovery, development, and translation of crosscutting, innovative approaches to analyzing the heterogeneity of biologically relevant populations of cells in situ. In June

[2152] https://commonfund.nih.gov/HuBMAP.
[2153] https://www.nih.gov/news-events/news-releases/nih-build-detailed-map-cells-within-human-body.

2017, the program announced the winners of the *Follow that Cell* prize competition.[2154,2155] Prizes were awarded for development of new tools and methods to predict the behavior and function of a single cell in complex tissue over time. The first-place winner developed a technique to noninvasively sample material inside the cell multiple times in the same cell, enabling scientists to track molecular changes over time or in response to treatments. The second-place winner took advantage of cell secretion pathways to access molecules of interest from inside the cell, demonstrating the ability of a cell to "self-report" gene activity.

To study the interactions among microorganisms and human cells—and for early identification of disease-causing microbes—NLM Intramural researchers have developed a fully automated mass spectrometry–based proteomics pipeline to identify microbes and their proteomics.[2156–2158] Induction of pluripotency in somatic cells has made a huge step forward for regenerative medicine and shows great potential as disease models and therapeutic agents. Many studies have shown that somatic cells can be reprogrammed to iPSCs. However, the underlying mechanism of the reprogramming process is not yet fully understood and may limit its usefulness. A better understanding of the molecular mechanism of reprogramming will help generate high-quality iPSCs and hopefully increase the efficiency of induction. Using a large set of gene expression data, NLM Intramural researchers have devised a model that utilizes a gene regulatory network in two steps.[2159] The network is first perturbed by forced overexpression of a few reprogramming factors and is driven from the initial steady state (somatic cell) to an intermediate steady state. The perturbation is then switched off, and the system relaxes to its final iPSC state.

In FYs 2016–2018, NIGMS also supported research to provide a detailed characterization of the changes in gene expression, chromatin, and metabolism that occur during conversion of somatic cells to iPSCs.

Many common and rare diseases are caused by changes to the genetic code. Genome editing technologies present an exciting prospect for treatments and possibly even cures for these diseases. The NIH Common Fund's Somatic Cell Genome Editing program, launched in 2018, aims to develop quality tools to perform effective and safe genome editing in human patients.[2160,2161] Somatic cells are any of the nonreproductive cells of the body (i.e., the cells do not pass DNA down to the next generation). By focusing on somatic cells, any changes to the DNA introduced by the genome editing therapeutics will not be inherited. The program is expected to expand the number of genome editing tools available to researchers, develop efficient and targeted delivery systems to direct editing tools to specific cells and tissues, and design new assays for testing safety and efficiency. Ultimately, the hope is that by making these tools widely available

[2154] https://commonfund.nih.gov/singlecell.
[2155] https://www.nih.gov/news-events/news-releases/nih-names-winners-follow-cell-phase-2-competition.
[2156] https://intramural.nih.gov/search/searchview.taf?ipid=106314&ts=1549481562.
[2157] Alves G, et al. *J Am Soc Mass Spectrom* 2018;29(8):1721-37. PMID: 29873019.
[2158] Joyce B, et al. *BMC Res Notes* 2018;11(1):182. PMID: 29544540.
[2159] Hamaneh MB and Yu Y-K, *PLoS One* 2019;14(8): e0220742. PMID: 31374103.
[2160] https://commonfund.nih.gov/editing.
[2161] https://www.nih.gov/news-events/news-releases/nih-launch-genome-editing-research-program.

to the research community, the time and cost required to develop new genome editing therapies will be reduced.

NIA intramural and extramural investigators collaborated to discover a more powerful predictor of aging than relying on chronological age. Using an innovative two-step process, they developed a new measure of aging called DNAm PhenoAge that strongly outperforms previous measures for predicting a variety of aging outcomes, including all-cause mortality, cancers, health span, physical functioning, and Alzheimer's disease.[2162] The measure is based on DNA modifications, called methylation, that can turn gene activity on or off. Methylation patterns are stable and can persist over decades, even across generations.

An NLM intramural investigator has shed light on understanding how mutational patterns in genes have an impact on cancers and how RNA binding motifs can aid in drug design. The analysis of the mutational landscape of cancer, including mutual exclusivity and co-occurrence of mutations, has been instrumental in studying the disease. BeWITH is a new method that enables extracting gene modules characterized by specific mutational patterns from large sets of patient data.[2163] The method investigates various aspects of cancer mutations, leading to the discovery of new relationships among mutated gene modules, cancer subtypes, and mutational signatures, all of which contribute to a better understanding of the key question of the mutational landscape of cancer. Also supported by NLM, AptaTRACE is a new approach to analyze hundreds of millions of RNA sequences obtained with HT-SELEX experiment (a laboratory technique that identifies short RNA molecules that bind to a target of interest).[2164] The method predicts RNA sequence structure–binding motifs that mediate RNA binding to the target. The target molecules used in HT-SELEX include molecules whose function needs to be modified for medical treatment purposes. Identification of the RNA binding motifs can aid in RNA-based drug design.

Scientists are strongly advocating for rigor and reproducibility in scientific data. NIGMS put forth a new initiative for better defining growth medium to improve reproducibility of cell culture. Fetal bovine serum is the most widely used growth supplement for cell culture because it cost-effectively supports the survival and growth of many cell lines. Although serum is an effective growth promotor, it is highly variable in its composition, activity, and physiological effects on cells. This variability introduces inconsistencies into cell culture research. This FOA will support small business projects to develop novel, reliable, and cost-effective tools that will make it easier for researchers to standardize or replace serum in cell culture.[2165]

Cutting-Edge Assays and Diagnostics

A critical component to receiving the best possible treatment relies on the ability to accurately detect and identify indicators and sources of potential health risks. Biomarkers can be used as measurable indicators of the severity or presence of a disease state. NICHD has supported several technological advances using the detection of biomarkers found in a patient's blood. For example, NICHD-funded researchers reported

[2162] Levine M, et al. *Aging* 2018;10(4):573-91. PMID: 29676998.
[2163] Dao P, et al. *PLoS Comput Biol* 2017;13(10). PMID: 29023534.
[2164] Dao P, et al. Cell Syst 2016;3(1):62-70. PMID: 27467247.
[2165] https://grants.nih.gov/grants/guide/pa-files/pa-18-815.html.

a new method that uses sound waves to isolate exosomes from blood. Exosomes are bubble-like particles excreted by cells, and they contain information that may be useful for monitoring or detecting various health conditions. However, the use of exosomes as biomarkers is limited by the ability to separate them from body fluid samples, such as blood, saliva, urine, and breast milk. According to the study team, the new acoustofluidic platform offers a simple, quick, and potentially cost-effective strategy to isolate exosomes.[2166]

Another example of the use of biomarkers to screen for injury or disease state is a new blood test developed by NICHD-supported researchers that can help identify bleeding in the infant brain. Abusive head trauma is the leading cause of death from physical abuse. Failure to diagnose this injury could lead to further brain damage or even death. However, many infants do not show obvious signs or may have nonspecific symptoms, such as vomiting. The research team developed a scoring system, based on blood levels of specific substances (biomarkers), that estimates the likelihood of bleeding in the brain.[2167] High scores indicate that a child should be referred for brain imaging to confirm the bleeding.

Assays can also be used to screen for compounds and contaminants in patient's blood and in the environment. Each year, tens of thousands of chemicals are manufactured in or imported into the U.S.—more than 30,000 pounds of industrial chemicals for every American—yet experts know little about which chemicals may enter people's bodies or how these substances affect human health.[2168] Scientists funded by NIEHS have found a way to screen people's blood for hundreds of chemicals at once, a method that will improve our ability to better assess chemical exposures in pregnant women, and to identify those exposures that may pose a health risk. The scientists used a technique known as high-resolution mass spectrometry, which identifies chemicals by their molecular weight, to screen blood samples taken from pregnant women in San Francisco. This enabled them to scan a much larger number of chemicals at once than previous methods, which typically target about a dozen chemicals at a time. They scanned about 700 chemicals in the current study, finding, on average, 56 different suspect chemicals in the women's blood.

Other NIEHS grantees, jointly funded by the National Science Foundation, are focusing on marine-related health issues through the Centers for Oceans and Human Health and through individual research projects that focus on oceans and human health, as well as the Great Lakes and human health.[2169,2170] Grantees are developing techniques for more accurate and earlier detection of harmful algal blooms, with the goal of preventing or reducing exposure. Grantees are also examining the health effects of consuming seafood containing such pollutants as PCBs and mercury, identifying indicators of recreational water contamination and illness, and exploring how climate change might affect the formation and transfer of methylmercury to the fish and shellfish that humans consume.

[2166] Wu M, et al. *Proc Natl Acad Sci USA* 2017;114(40):10584-9.
[2167] Berger RP, et al. *JAMA Pediatr* 2017;171(6):e170429.
[2168] https://www.ucsf.edu/news/2018/07/411186/scientists-develop-new-method-screen-chemical-exposures.
[2169] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-16-009.html.
[2170] https://www.niehs.nih.gov/research/supported/centers/oceans/index.cfm.

In addition to screening for compounds in our water and in our patients, scientists routinely use archived tissue samples as resources for conducting research. NIEHS' SBIR grants support the development of novel technologies to expand the capability for molecular analyses of banked frozen or formalin-fixed, paraffin-embedded tissues.[2171] The need exists for improved tissue preservation methods that maintain histologic features while preserving high-quality DNA, RNA, protein and small molecules in archived tissue from rodent and human studies. In addition, novel approaches are needed to preserve DNA, RNA, and small molecules during collection and storage of biological samples. Maintaining the integrity of these cellular components will vastly improve scientists' ability to obtain molecular information from archived tissue samples, which serve as a valuable resource for research studies due to their wide availability and propensity for decades of use.

The power of biomedical technologies lies not only in their immediate applicability but in their potential for use as a foundation for further development and applicability. For example, as part of NCCIH's small business grant programs, the Center is leveraging existing biotechnologies in an effort to increase the efficiency of research on methods development in natural products chemistry by adapting existing biotechnologies to advance natural products research. Innovative methods supported by two FOAs issued in 2016 aim to utilize genomics, bioproducts engineering, bioinformatics, synthetic and molecular biology, or nanotechnology.[2172]

Research Resources and Infrastructure

To fulfill its mission, it is critical for NIH to develop, maintain, and renew scientific human and physical resources that will ensure the nation's capability to prevent disease. Therefore, storing, managing, standardizing, and publishing the vast amounts of data produced by biomedical research is of critical importance to NIH, which directs programs for the collection, dissemination, and exchange of information in medicine and health. The information and ideas that NIH shares with the biomedical research community and public, along with the advances in computational science and general capacity building, serve as the foundation upon which NIH advances knowledge to improve the lives and health of Americans. By focusing on capacity building and strengthening the resources and infrastructure for conducting research, NIH capitalizes on its investment in biomedical research.

Summary of NIH Activities

NIH's approach to establishing and maintaining research resources and infrastructure builds on the bedrocks of sharing information, data, and research models and samples. To ensure that research resources developed with NIH funding are made readily available to the research community for further study, NIH supports (1) networks, centers, and consortia to share these resources and work together

[2171] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-16-012.html.
[2172] https://grants.nih.gov/grants/guide/pa–files/PA-16-342.html.

toward common goals; (2) developments in data and computational science to drive innovation and advance research in human health and disease; and (3) capacity building to capitalize on the research opportunities of the future.

NIH is pioneering ways to make research resources, such as biological samples and data, accessible and secure. The use of repositories, databases, and data sharing maximizes the value of research funded and generated by NIH and accelerates the pace of biomedical discovery and medical breakthroughs. Additionally, the use of repositories and databases can increase scientific rigor and reproducibility, enable meta-analyses, and increase the transparency of research and research data. NIH has a large and growing number of valuable repositories and databases and is continually building tools for better management of research, personal health, and big data. NLM houses many of NIH's databases and biomedical information services, such as the widely used PubMed, and numerous ICs maintain their own databases and resources for data sharing, as well. Some of NIH's key databases and data-sharing efforts for FY 2016–2018 are highlighted below.

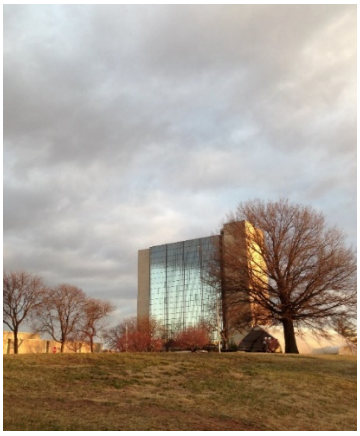

Figure 128. Established by a joint resolution of Congress in 1968, the Lister Hill Center for Biomedical Communications is a research and development division of the National Library of Medicine. Credit: Lydia Polimeni, NIH.

Databases and Data Sharing

In NIH's view, all data should be considered for data sharing. To that end, the NIH Data Sharing Policy was implemented in 2003. Data sharing promotes many goals of the NIH research endeavor and is vital for unique data that cannot be readily replicated. In 2016, NIH developed Common Data Elements (CDE) to standardize the collection, terminology, variables, and measures to be used in NIH-funded clinical research, enabling greater reproducibility and meta-analyses.[2173] Data sharing allows scientists to expedite the translation of research results into knowledge, products, and procedures to improve human health.

Sharing data from NIH-supported studies has many benefits. Data sharing reinforces open scientific inquiry, encourages diversity of analysis and opinion, promotes new research, makes possible the testing

[2173] https://www.nlm.nih.gov/cde/index.html.

of new or alternative hypotheses and methods of analysis, supports studies on data collection methods and measurement, facilitates the education of new researchers, enables the exploration of topics not envisioned by the initial investigators, and permits the creation of new datasets when data from multiple sources are combined.

Storing, managing, standardizing, and publishing the vast amounts of data produced by biomedical research is of critical importance to NIH. Research resources and infrastructure, such as powerful databases, are necessary for this endeavor to succeed.

NLM supports many of NIH's databases and biomedical information resources. PubMed, NLM's most heavily used database, contained records for more than 29.1 million life science and biomedical journal articles at the end of 2018.[2174] NLM added more than 1.2 million new citations to PubMed in FY 2018. Of those citations, 904,636 were indexed for MEDLINE—the largest subset of PubMed citations—using NLM's controlled vocabulary, Medical Subject Headings. Indexing adds value to the citation and abstract by adding subject headings; classifying certain types of research (e.g., clinical trial, systematic review); and improving links to related information (e.g., datasets). NLM also launched a 5-year initiative to explore novel approaches to automated indexing.

In FY 2018, NLM enhanced its procedures to accept small datasets related to articles in PubMed Central (PMC) from NIH-funded researchers to facilitate their discovery and reuse. The NIH Public Access Policy ensures that the public can access—without charge—peer-reviewed journal articles arising from NIH-funded research. Since 2008, the PMC database has served as the repository for journal articles subject to the NIH Public Access Policy. NIH is collaborating with five divisions and Offices in HHS and five agencies outside HHS to use PMC and related services in support of their public access policies. Interagency agreements have been signed with AHRQ, CDC, FDA, ACL, and the Office of the Assistant Secretary for Preparedness and Response within HHS, as well as with EPA, VA, the National Aeronautics and Space Administration (NASA), National Institute of Standards and Technology, and the U.S. Department of Homeland Security. Researchers either employed or funded by these agencies have started depositing manuscripts in PMC.

At the end of 2018, nearly one million NIH-funded articles had been deposited in PMC to be made accessible to the public without subscription, fees, or other barriers.[2175] Free availability of these papers is useful to a wide range of people who might not otherwise have access, including researchers conducting studies, clinicians looking for medical information, patients and their friends and family seeking information about a medical condition, students and educators, and librarians assisting others in information retrieval. The available public access papers have been retrieved in PMC more than one billion times, illustrating the global impact of NIH research on advancing science and improving human health (around 4 percent are currently under an embargo of 12 months or less).

[2174] https://www.ncbi.nlm.nih.gov/pubmed.
[2175] https://www.ncbi.nlm.nih.gov/pmc/.

NICHD developed and implemented the Data and Specimen Hub as a centralized resource for researchers to store and access data from NICHD-funded research studies to use for secondary research.[2176,2177] The Hub serves as a mechanism for NICHD-funded extramural and intramural investigators to share research data from studies in accordance with the NIH Data Sharing Policy and the NIH Genomic Data Sharing Policy (introduced in 2015).

Similarly, the goal of NIEHS' Children's Health Exposure Analysis Resource is to provide the research community with access to data and to laboratory and statistical analyses to improve our knowledge of the comprehensive effects of environmental exposures on human health throughout the life course. In FY 2017, five FOAs were posted to support the development of community-based data and metadata standards and new technologies.[2178– 2182]

NLM also developed and operates the database of Genotypes and Phenotypes (dbGaP)—which, as of 2018, contains more than 1,200 studies with de-identified genomic and phenotypic (clinical observation) data on more than 2 million subjects. NIH introduced dbGaP and the GWAS policy in 2007 to facilitate controlled access to GWAS data based on participants' informed consent. Following the changes to data management procedures under the NIH Genomic Data Sharing Policy, dbGaP now allows unrestricted access to summary-level genomic results from studies marked as nonsensitive via the PheGenI tool.[2183,2184] Individual-level data can be accessed only after approval of a controlled data access application that states research objectives and demonstrates the ability to protect the data adequately.[2185] These policies provide unprecedented access to large genetic and phenotypic datasets funded by NIH and other agencies worldwide.[2186]

More to that point, NHLBI's Trans-Omics for Precision Medicine (TOPMed) program is creating one of the most diverse resources of its kind, aggregating genomic, environmental, clinical, and imaging data from about 150,000 diverse individuals enrolled in more than 60 cohort studies to shed light on disease mechanisms and potentially reveal new therapeutic targets for heart, lung, blood, and sleep disorders.[2187–2189] The first set of nearly 9,000 genome sequences was released to eligible researchers

[2176] Hazra R, et al. *Sci Data* 2018;5:180046. PMID: 29557977.
[2177] https://dash.nichd.nih.gov/.
[2178] https://grants.nih.gov/grants/guide/rfa-files/rfa-es-18-010.html.
[2179] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-18-014.html.
[2180] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-18-011.html.
[2181] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-18-012.html.
[2182] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-18-013.html.
[2183] https://www.ncbi.nlm.nih.gov/gap/phegeni.
[2184] Note that this policy change was announced on November 1, 2018, which is just outside the reporting period for this triennial. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-023.html.
[2185] https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=login.
[2186] https://www.ncbi.nlm.nih.gov/gap.
[2187] https://www.nhlbi.nih.gov/news/2016/toward-precision-medicine-first-whole-genomes-topmed-now-available-study.
[2188] https://www.nhlbi.nih.gov/science/trans-omics-precision-medicine-topmed-program.
[2189] https://www.nhlbiwgs.org/.

through dbGaP in October 2016. More data samples from TOPMed continue to be released on dbGaP and made available to the scientific community.

Data sharing is essential to expedite translation of research results into knowledge, products, and procedures to improve human health. For example, NHGRI intramural investigators have established the *Atlas of Human Malformation Syndromes in Diverse Populations*, which is the first online photographic atlas for diagnosing people with various genetic diseases from different parts of the world.[2190–2192] Most clinicians around the world have been trained with clinical genetic resources that used patients of northern European descent as the standard of reference, so the *Atlas* will be useful in diagnosing congenital abnormalities, which are a global leading cause of death in newborns in populations around the world.

In addition, NHGRI, along with NICHD and NLM, created ClinVar, a public database where genomic testing laboratories around the world can submit reports of genomic variants with accompanying clinical information and interpretation.[2193] Investigators working on the Clinical Genome Resource (ClinGen) define and disseminate the clinical relevance of genomic variants that are reported to ClinVar.[2194] The ClinGen project was renewed for an additional four years in 2017 and will work on defining the clinical relevance of variants related to pediatric neurology, hematology, and skin diseases.

Data sharing must also evolve as the types of data and users evolve. ODS, in partnership with NLM, has developed the Dietary Supplement Label Database (DSLD), a free web-based resource that aims to compile all information from the labels of dietary supplements marketed in the U.S.[2195,2196] This database includes contents, ingredient amounts, and any health-related product statements, claims, and cautions. The DSLD currently contains 86,000 labels and is expected to grow rapidly over the next three years to include most of the estimated 100,000+ dietary supplement products sold to American consumers. In October 2016, ODS published a *Federal Register* notice requesting ideas and suggestions on how the DSLD might evolve—such as what features might be added, improved, or enhanced. For example, changes in capabilities related to search, sorting, organization, and downloading of information would make it a more valuable tool for users. A federal stakeholder panel for the DSLD is working with developers to make key changes to improve functionality.

In FY 2017, NIH launched the Data Commons Pilot Phase, supported by the NIH Common Fund, to accelerate biomedical discoveries by making biomedical research data findable, accessible, interoperable, and reusable (FAIR) for more researchers.[2197] Completed in FY 2018, the tools and best practices

[2190] https://www.nih.gov/news-events/news-releases/nih-creates-atlas-human-malformation-syndromes-diverse-populations.
[2191] https://research.nhgri.nih.gov/atlas/.
[2192] Muenke M, et al. *Genet Med* 2016;18(11):1085-7. PMID: 26938780.
[2193] https://www.ncbi.nlm.nih.gov/clinvar/.
[2194] https://www.clinicalgenome.org/.
[2195] https://dsld.nlm.nih.gov/dsld/.
[2196] Dwyer JT, et al. *J Acad Nutr Diet* 2014;114(10):1512-7. PMID: 24928780.
[2197] https://www.nih.gov/news-events/news-releases/nih-awards-test-ways-store-access-share-compute-biomedical-data-cloud.

developed by the Data Commons Pilot Phase will inform a broader trans-NIH data ecosystem strategy. The NIH Common Fund will continue to test, evaluate, and refine a subset of deliverables from the Data Commons Pilot Phase, working with other Common Fund programs to establish a cloud-based data ecosystem for Common Fund datasets.

Several ICs are working toward the common goal of making shared biomedical research data FAIR. For example, NHGRI's Genomic Data Science Analysis, Visualization, and Informatics Lab-space (AnVIL), launched in FY 2018, is a cloud-based, interoperable platform for data storage, analysis, and management. The goal is to provide researchers with more powerful abilities to access, integrate, and analyze large genomic datasets, empowering the broader research community to gain new insights about human health and disease.[2198] AnVIL will help researchers store, access, and analyze the large amounts of data being generated from genome sequencing.

In close collaboration with the Office of the National Coordinator for Health Information Technology and other federal departments and agencies, NLM develops, funds, and disseminates the clinical terminologies and coding systems designated as U.S. standards to promote interoperability and health information exchange. NLM also supports the development, maintenance, and distribution of the tools and resources needed to implement health data standards. For example, in FY 2018, NLM successfully migrated to a new set of tools for authoring, mapping, handling content requests, and producing SNOMED CT, which is a suite of designated standards for use in U.S. federal government systems for the electronic exchange of clinical health information.[2199] This migration increased efficiency and productivity while reducing maintenance costs. In addition, in FY 2018, the use of NLM's RxNav—a graphical interface and applied programming interface to facilitate access to drug terminologies by researchers, industry, and the public—reached a new high of one billion queries.[2200] NLM also added new attributes to better align RxNorm, which provides normalized names for clinical drugs, with global drug information standards to improve global interoperability for medicinal products.[2201]

To increase the efficiency and effectiveness of clinical research studies, cerebral palsy–specific CDEs were developed through a partnership between NINDS and the American Academy of Cerebral Palsy and Developmental Medicine.[2202,2203] International experts reviewed existing NINDS CDEs and tools used in studies of children and young people with cerebral palsy. CDEs were compiled, subjected to internal review, and posted online for external public comment in September 2016. This collection of CDEs for cerebral palsy is now publicly available in the NIH CDE Repository, a research resource developed and managed by NLM.[2204] The global use of CDEs for cerebral palsy will standardize data collection, improve

[2198] https://www.genome.gov/27569268/genomic-analysis-visualization-and-informatics-labspace-anvil/.
[2199] https://www.nlm.nih.gov/healthit/snomedct/index.html.
[2200] https://rxnav.nlm.nih.gov/.
[2201] https://www.nlm.nih.gov/research/umls/rxnorm/index.html.
[2202] Schiariti V, et al. *Dev Med Child Neurol* 2018;60(10):976-86. PMID: 29542813.
[2203] https://www.commondataelements.ninds.nih.gov/cerebral%20palsy.
[2204] https://cde.nlm.nih.gov/home.

data quality, facilitate comparisons across studies, and more effectively aggregate information into significant metadata results.

Similarly, to maximize the impact of its HIV/AIDS and drug addiction research portfolios, NIDA encourages its investigators to use common measures across studies so datasets can be combined to address novel research questions with enhanced statistical power and the ability to detect more subtle and complex associations among variables.[2205] This successful effort to harmonize HIV/AIDS and drug addiction research has promoted greater collaboration among R01 investigators, enhanced the efficiency of research, and increased NIH's return on investment.

Data Science and Computational Science

Data science is the interdisciplinary field of inquiry in which quantitative and analytical approaches, processes, and systems are developed and used to extract knowledge and insights from increasingly large and/or complex sets of data. Data science involves obtaining insights, information, and value from data. Computational biology is the science of using biological data to develop and apply innovative algorithms and tools, models, data-analytical methods, and computational simulation techniques to understand biological systems and relationships. NIH has an immense and incredibly strong biomedical data science and computational biology ecosystem. Often these studies result in novel methodologies that improve health care, clinical diagnoses, and existing standards of care.

In June 2018, NIH released the final draft of its Strategic Plan for Data Science to provide a roadmap for modernizing the NIH-funded biomedical data science ecosystem.[2206] The four main objectives are to address the findability, interconnectivity, and interoperability of NIH-funded biomedical datasets and resources; the integration of existing data management tools and development of new ones; the universalization of innovative algorithms and tools created by academic scientists into enterprise-ready resources that meet industry standards of ease of use and efficiency of operation; and the growing costs of data management.

Supporting Innovation

Funding opportunities, such as through the NIH Common Fund's previous program for Bioinformatics and Computational Biology, are one way that NIH has bolstered its strong biomedical data science and computational biology ecosystem.

NLM is one IC making use of focused funding announcements to target areas of research that are important to its mission and broader NIH interests in data science. For example, in 2018, NLM launched a new initiative to apply data science approaches to help consumers gather, manage, use, and understand information about their personal health.[2207] Five newly funded research awards in FY 2018 will create

[2205] https://www.drugabuse.gov/research/research-data-measures-resources/data-harmonization-projects.
[2206] https://www.nih.gov/news-events/news-releases/nih-releases-strategic-plan-data-science.
[2207] https://www.nlm.nih.gov/ep/GrantPHLConsPat.html.

tools for patients and caregivers to better manage chronic conditions, including diabetes and epilepsy; self-tracking tools (e.g., activity and symptom sensors) to capture a more complete, accurate, and longer-term understanding of an individual's health and improve self-management and clinical care; and a smartphone application to help motivate and enable African American and Hispanic patients to assemble and use prevention-focused personal health libraries.

Additionally, in FY 2018, NLM launched a new initiative to support computational approaches to curation at scale for biomedical research assets. Awards will support novel informatics and data science approaches for increasing speed and availability and for ensuring the quality of automated annotation, storage, and retrieval of secure biomedical research resources (e.g., data, images, computational models), which can serve as the basis of transformative biomedical discoveries by improving the speed and scope of the curation processes.[2208]

Through another funding opportunity, research project grants (RPG), NLM supports pioneering research and development to advance biomedical informatics and data science, including methods for extracting the meaning from data, such as the data from genomic sequences or clinical data from EHRs. In FY 2018, NLM issued 29 new RPGs, including six exploratory and developmental awards. Innovation in data science was a research priority, representing more than 60 percent of funded research grants. In support of the NIH Next Generation Researcher Initiative, NLM awarded RPGs to 10 early-stage investigators. Four new awards in translational bioinformatics funded research projects focused on molecular interaction, gene regulation, genetic variants and neuroanatomical shape, and alterations of gene expression patterns. NLM also issued an administrative supplement to the NIH HEAL Initiative.

In alignment with the NIH Strategic Plan for Data Science, NIGMS investments in computational data sciences focus on using optimal techniques in computer and data sciences to address problems in biology and medicine.[2209] From FY 2016 to 2018, NIGMS supported computational research into methods and algorithms for the design of new therapeutics. By funding areas of science that integrate and analyze diverse sets of experimental data, together with computational simulations, researchers were able to create more effective drug candidates that could have fewer adverse effects.

Tools and Technological Approaches

Data science, and the tools and technological approaches that it has generated, enables researchers to query large sets of patient data across institutional boundaries, conduct predictive clinical analytics, and answer important biomedical research questions through observational and pragmatic clinical trial approaches.

In 2017, NLM and its National Network of Libraries of Medicine (NNLM) announced *NNLM RD3: Resources for Data-Driven Discovery* to support access to biomedical and health information with the goal of making

[2208] https://www.nlm.nih.gov/ep/GrantDigCur.html.
[2209] https://datascience.nih.gov/strategicplan.

data discoverable, accessible, and citable.[2210] This tool has served as a resource for librarians, library students, information professionals, and interested individuals to learn about and discuss such topics as library roles in data science, fundamentals of domain sciences, and emerging trends in supporting biomedical research. The resource supports advancing data science, open science, and biomedical informatics through aggregate data resources, programs, and services across the NNLM.

Like all areas of science, data science requires and benefits from a collaborative approach. For example, in FY 2018, NLM provided technical expertise and collaborative assistance to CIT to establish trans-NIH authentication and authorization services for user access to research data hosted on multiple cloud providers in support of NIH-wide initiatives in data science. NLM also provided technical leadership into activities that support the NIH New Models of Data Stewardship program, including the NIH Strategic Plan for Data Science and the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative.

Computational de-identification seeks to develop tools that will automatically remove all of the personal identifiers, patient names and names connected to the patient, dates, and such identifiers as hospital numbers and accession numbers from the clinical narrative text.[2211] This tool also aims to understand the statistics and issues surrounding such removal, with the goal of generating de-identified documents that can be used in clinical research while protecting patient privacy. In 2018, a faster, reentrant version of the NLM Scrubber was released, which also provides better preservation of scientific information and privacy.[2212] The NLM Scrubber team is actively collaborating with several research groups that helped to modify the software to work on de-identifying 2 billion VA records and more than 100,000 radiology reports.

Artificial Intelligence and Machine Learning

Artificial intelligence and machine learning are advancing rapidly and are used across industries, including biomedical research and health care delivery. Machine learning is by no means new—it has been around for decades—but thanks to big data and more powerful computers, it has evolved into an amazing tool that has helped to advance—and often speed up—scientific research. In machine learning, computer systems automatically learn from experience without being explicitly programmed. A computer program analyzes data to look for patterns, determines the complex statistical structures that identify specific features, and then finds those same features in new data.

In September 2017, the NIH CC released more than 100,000 anonymized chest X-ray images and their corresponding data to the scientific community. The release will allow researchers across the country and around the world to freely access the datasets and increase their ability to teach computers how to detect

[2210] https://nnlm.gov/data.
[2211] Kayaalp M. *Balkan Med J* 2018; 35(1):8-17. PMID: 28903886.
[2212] https://scrubber.nlm.nih.gov/Announcement.2018-12-31.html.

and diagnose disease. Ultimately, this artificial intelligence mechanism can lead to clinicians' making better diagnostic decisions for their patients.[2213]

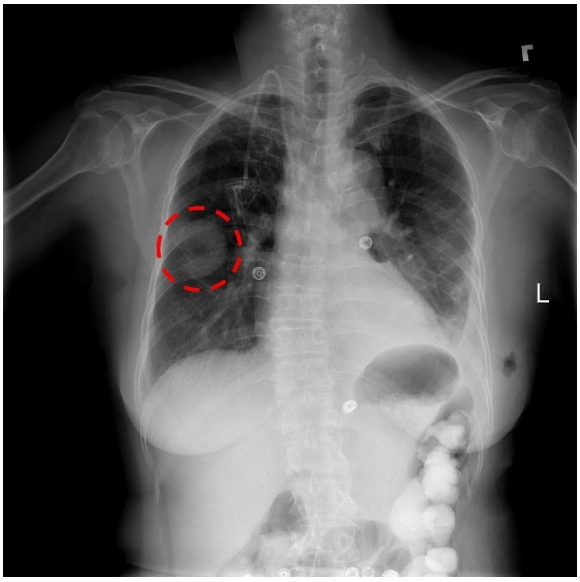

Figure 129. Chest X-ray showing a lung mass. Credit: NIH.

To fulfill its mission, ODP systematically monitors NIH investments in applied prevention research—in other words, research on primary and secondary prevention methods in patients, as well as prevention-related methods. Currently, NIH uses the Research, Condition, and Disease Categorization system to report agency funding in prevention research. However, this system defines prevention research broadly to include primary and secondary prevention, studies on prevention methods, and basic and preclinical studies for prevention. A new methodology was needed to quantify NIH funding in applied prevention research. A novel machine-learning approach was developed and evaluated for its ability to characterize NIH-funded applied prevention research conducted in FY 2012–2015.[2214]

With the increasing availability of text information related to diverse research fields across NIH, the domain of biomedical text mining and NLP has seen a tremendous growth. Furthermore, text mining techniques are core to computational biology, including genomics and other -omics analysis.

NLM researchers develop and test advanced text mining techniques that can be used, for example, to improve the retrieval of biomedical information from NLM databases and analyze unstructured clinical text in EHR data. In FY 2018, several studies were published that demonstrated the potential of NLP techniques to enable broader use of EHRs as a source of data for clinical research and natural history

[2213] The causes of these diseases can be difficult to decipher because they result from a complex combination of genomic influences and environmental factors.
[2214] Villani J, et al. *Am J Prev Med* 2018;55(6):926-31. PMID: 30458951.

studies, to evaluate the feasibility of a clinical trial design, and to assess adverse events and risks associated with drug exposure in post-market observational studies.[2215–2218]

In addition, a project funded by NLM used data from EHR systems and computational approaches for collecting information related to social, behavioral, and familial factors for subsequent analyses to enhance the understanding of how these factors interact in patients with specific health conditions.[2219–2221]

Approaches to Genetics and Genomics

Today, advances in tools and techniques for data generation are rapidly increasing the amount of data available to researchers, particularly in genomics. This increase requires researchers to rely ever more heavily on computational and data science tools for the storage, management, analysis, and visualization of data. NIH researchers are using data science and computational approaches in innovative ways to study genetics and genomics in basic biology and biochemistry, evolution, physiology, cancer, biotechnology, and clinical research.

Patterns or motifs that are shared among multiple DNA or protein sequences often correlate with important biological functions. NLM conducts research on methods, measures, and statistics for the comparison and analysis of DNA and protein sequences and on how to model those relationships to elucidate protein subfamily functions. A widely used method for representing and studying such patterns is provided by sequence logos, which are a graphical representation of an amino acid or nucleic acid. NLM developed and made the LogOddsLogo program freely available for other researchers to use to conduct such analyses.[2222,2223]

Efforts also are ongoing to improve and extend the functionality of current approaches and tools. For example, an important task in a metagenomic analysis is the assignment of taxonomic labels to sequences in a sample.[2224] The BLAST family of protein and DNA database search programs constitute one of the key services offered by NLM—illustrated by the fact that these programs are currently run on NLM servers about 200,000 times during a typical weekday.[2225,2226] To optimize the results or hits from BLAST searches, researchers developed and tested a two-step approach for metagenomic taxon identification, where

[2215] Kayaalp M, et al. *AMIA Annu Symp Proc* 2018;2017:1044-50. PMID: 29854172.
[2216] Kilicoglu H, et al. *J Am Med Inform Assoc* 2018;25(7):855-61. PMID: 29718377.
[2217] Rodriguez LM, et al. *AMIA Annu Symp Proc* 2018;2017:1498-1506. PMID: 29854219.
[2218] Demner-Fushman D, et al. *Sci Data* 2018; 5:180001. PMID: 29381145.
[2219] https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8917296.
[2220] Winden TJ, et al. *AMIA Jt Summits Transl Sci Proc* 2018; 2017:236-45. PMID: 9888079.
[2221] Winden Tj, et al. *AMIA Annu Symp Proc* 2018;2017:1783-92. PMID: 29854249.
[2222] Yu YK, et al. *Bioinformatics* 2015;31(3):324-31. PMID: 25294922.
[2223] https://www.ncbi.nlm.nih.gov/CBBresearch/Yu/logoddslogo/.
[2224] Altschul SF, et al. Handbook of Discrete and Combinatorial Mathematics. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2017 Nov. 20.1.
[2225] https://intramural.nih.gov/search/searchview.taf?ipid=106305&ts=1549481562.
[2226] NCBI Resource Coordinators. *Nucleic Acids Res* 2018;46(D1):D8-D13. PMID: 29140470.

sequences are first classified using a reference database and then a more complex phylogenetic method is used to classify sequences that were not classified in the first step.[2227]

A rapidly growing database of completely or nearly completely sequenced genomes of bacteria, archaea, eukaryotes, and viruses (more than 100,000 genomes already available and many others in progress) creates both new opportunities and major new challenges for genome research. In 2017, NLM focused efforts on a project that aimed to establish fundamental principles of genome evolution and function by taking advantage of available genomic information.[2228] In a number of studies, researchers developed new computational and mathematical methods, explored patterns of gene inheritance and gene transfer to genome evolution, and discovered novel groups of organisms.[2229– 2235] These studies advance understanding of the general principles and specific aspects of genome evolution in diverse life forms—in particular, viruses and mobile elements—as well as cancer genome evolution.

In a complex multiyear, multi-institute collaboration, researchers characterized genetic variants in the Framingham Heart Study population that were associated with the differential expression of protein-coding genes, providing insights into the molecular regulatory patterns involved in human physiology and pathophysiology.[2236] This integrated GWAS enables new uses of this well-known federal investment for further research purposes.

Among the most pressing issues in interpreting the large-scale data produced by genomics studies on cancer is the identification of mechanisms of mutagenesis in cancer cells. Researchers supported by NCI, NLM, and other collaborators developed the computational framework for the online server, MutaGene, which analyzes sets of cancer mutations to determine the most likely process by which the genetic information was changed and to identify cancer type and cohorts of patients with similar genetic mutation signatures.[2237– 2242] Additionally, researchers are developing a new computational method to extract sets of related genes characterized by specific mutational patterns (for example, patterns known to occur in

[2227] Shah N, et al. *Algorithms Mol Biol* 2018;13:7. PMID: 29588650.
[2228] https://intramural.nih.gov/search/searchview.taf?ipid=106311&ts=1549481562.
[2229] Galperin MY, et al. *J Bacteriol* 2018;200(7). pii: e00681-17. PMID: 29263101.
[2230] Krupovic M, et al. *Virus Res* 2018;244:181-93. PMID: 29175107.
[2231] Shmakov SA, et al. *Proc Natl Acad Sci U.S.A.* 2018; 115(23):E5307-16. PMID: 29784811.
[2232] Yutin N, et al. *Virol J* 2018; 15(1):67. PMID: 29636073.
[2233] Yutin N, et al. *Nat Microbiol* 2018;3(1):38-46. PMID: 29133882.
[2234] Ferrer M, et al. *Genes (Basel)* 2018;9(2). pii: E28. PMID: 29360740.
[2235] Amarasinghe GK, et al. *Arch Virol* 2018; 163(8):2283-94. PMID: 29637429.
[2236] Joehanes R, et al. *Genome Biol* 2017;18(1):16. PMID: 28122634.
[2237] https://intramural.nih.gov/search/searchview.taf?ipid=106329&ts=1549481562.
[2238] Zhao F, et al. *Int J Mol Sci* 2018;19(7). PMID: 30037003.
[2239] Xiao H, et al. *Genes Dev* 2017; 31(19):1958-72. PMID: 29074736.
[2240] Shaytan AK, et al. *Nucleic Acids Res* 2017;45(16):9229-43. PMID: 28934480.
[2241] Concearenco A, et al. *Nucleic Acids Res* 2017;45(W1):W514-22. PMID: 28472504.
[2242] Concearenco A, et al. *Methods Mol Biol* 2017;1647:221-36. PMID: 28809006.

cancer) from large sets of patient data.[2243–2245] By understanding the processes by which mutations arise and how specific gene mutations and cancer are related, researchers hope to better understand the mutational landscape of cancer and use this information to predict patient prognosis and response to treatment.

In the last few years, the rapid accumulation of genome sequences and protein structures has been paralleled by major advances in sequence and structure database search methods. These advances have expanded the tools and application of the gene editing toolbox. For example, NLM researchers have performed extensive mining of genomic and metagenomic sequence databases in search of novel viruses and antivirus defense systems to build off of our current CRISPR/Cas systems.[2246– 2251] These analyses have substantially expanded the known diversity of both viruses and defense mechanisms. Additionally, researchers have developed computational methods to discover a new class of CRISPR/Cas proteins classified based on microbial adaptive immune systems.[2252] These studies substantially expanded the collection of protein domains that are required for virus reproduction and host defense functions. These findings have potential implications for human health and developments in biotechnology.[2253,2254]

Computational methods are also at the forefront of advancing our understanding of diseases that affect both humans and plants and are providing critical insights into aging and other biological functions. NLM intramural researchers discovered enzymes and pathways critical to the origins and evolution of nucleotide-dependent signaling, which can affect DNA repair notably later in life. The researchers used sequence analyses with comparative genomics and other computational data visualization techniques to study the evolution and biochemistry of proteins and of whole systems at the organism level.[2255] This work led to the discovery of enzymes responsible for epigenetic modification of DNA via oxidation, a unified

[2243] Rogozin IB, et al. *Brief Bioinform* 2018;19(6):1085-1101. PMID: 28498882.
[2244] Rogozin IB, et al. *Cell Cycle* 2018;17(3):348-55. PMID: 29139326.
[2245] Li M, et al. *Methods Mol Biol* 1550:235-60. PMID: 28188534.
[2246] https://intramural.nih.gov/search/searchview.taf?ipid=106310&ts=1549481562.
[2247] Hudaiberdiev S, et al. *BMC Evol Biol* 2017;17(1):232. 29179671.
[2248] Krupovic M, et al. *Virus Res* 2018;244:181-93. PMID: 29175107.
[2249] Shmakov SA, et al. *Proc Natl Acad Sci U.S.A.* 2018;115(23):E5307-16. PMID: 29784811.
[2250] Yutin N, et al. *Virol J* 2018;15(1):67. PMID: 29636073.
[2251] Yutin N, et al. *Nat Microbiol* 2018; 3(1):38-46: PMID: 29133882.
[2252] https://intramural.nih.gov/search/searchview.taf?ipid=106310&ts=1549481562.
[2253] Ferrer M, et al. *Genes (Basel)* 2018;9(2). PMID: 29360740.
[2254] Galperin MY, et al. *J Bacteriol* 2018;200(7). PMID: 29263101.
[2255] https://intramural.nih.gov/search/searchview.taf?ipid=106318&ts=1549481562.

mechanism for nucleotide-based regulation of animal immune response and prokaryotic CRISPR systems, and novel toxin systems deployed in inter-organismal biological conflicts. [2256–2268]

The Secondary Genomics Finding Service (SGFS) is a team-based clinical service provided by NHGRI to intramural researchers using exome/genome sequencing to accomplish their research goals.[2269] The SGFS will analyze de-identified research exome/genome data for the presence of possible actionable secondary variants, which are genomic variants that are clinically useful but fall outside of the researchers' primary research interest. Any secondary variants found in the research data will be clinically confirmed because they could be important to research participants' health. The SGFS will coordinate confirmatory samples and provide genetic counseling and results disclosure to participants with secondary findings.

Repositories and Biobanks

A biobank is a repository that stores and manages biological samples known as biospecimens for use in research. Repositories and biobanks support the collection, analyses, storage, and distribution of biospecimens, which can include DNA, cell lines, or even such model organisms as zebrafish for research use. To promote data sharing as an essential element in biomedical research, NIH maintains and supports many repositories and biobanks and continues to generate insights from existing facilities.

The NIGMS Human Genetic Cell Repository at the Coriell Institute for Medical Research in Camden, New Jersey, contains more than 11,300 cell lines and 5,700 DNA samples derived from a diverse collection of healthy individuals and individuals with various inherited diseases.[2270] In FY 2016–2018, the demand for cell and DNA samples from the collection remained strong, with more than 5,000 cell samples and 34,000 DNA samples distributed per year.

[2256] Burroghs AM, et al. *Cell Cycle* 2017;16(11):1093-1103. PMID: 28441108.
[2257] Gendrin C, et al. *J Infect Dis* 2018;217(6):983-7. PMID: 29244079.
[2258] Gopalakrishnan AM, et al. *MBio* 2017;8(4). PMID: 28851851.
[2259] Holland SJ, et al. *Proc Natl Acad Sci U.S.A.* 2018;115(14):E3211-20. PMID: 29555777.
[2260] Iyer LM, et al. *J Bacteriol* 2017; 199(15). PMID: 28559295.
[2261] Kaur G, et al. *Sci Rep* 2018;8(1):6196. PMID: 29670199.
[2262] Krishnan A, et al. *Proc Natl Acad Sci U.S.A.* 2018;115(14):E3201-10. PMID: 29555751.
[2263] Li J, et al. *Science* 2017;355(6331):1312-7. PMID: 28336669.
[2264] Neuwald AF, et al. *Elife* 2018;7. PMID: 29336305.
[2265] Oakley MS, et al. *PLoS One* 2018;13(7):e0201043. PMID: 30044851.
[2266] Pusapati GV, et al. *Dev Cell* 2018;44(1):113-29.e8. PMID: 29290584.
[2267] Pusapati GV, et al. *Dev Cell* 2018;44(2):271. PMID: 29401421.
[2268] Verma R, et al. *Nature* 2018;557(7705):446-51. PMID: 29632312.
[2269] https://www.genome.gov/27567061/secondary-genomics-findings-service/.
[2270] https://www.nigms.nih.gov/Research/SpecificAreas/HGCR/Pages/default.aspx.

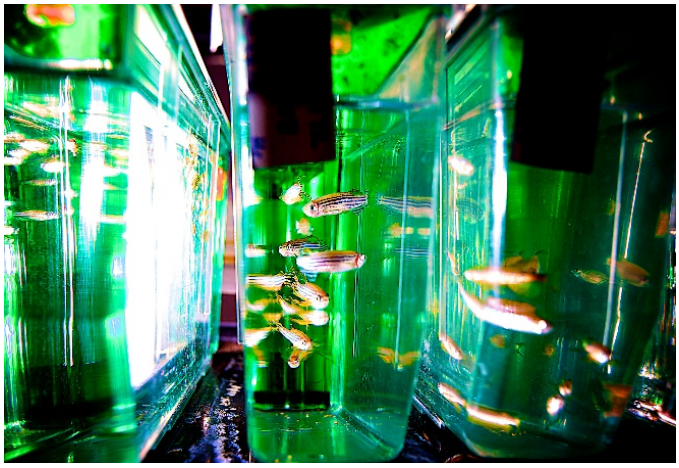

Figure 130. The NIH Zebrafish Facility is the largest in the world, with enough space for 19,000 tanks to accommodate 100,000 fish. Credit: Uri Manor, NICHD.

ORIP and NICHD support the Zebrafish International Resource Center (ZIRC), a repository of more than 30,000 wild-type and mutant strains of zebrafish used in research laboratories around the world.[2271] ZIRC includes a range of pathology and consultation services and information about zebrafish husbandry and research.[2272] ZIRC's existence is invaluable because zebrafish have been used in advances across the spectrum of biomedical research—from cancer and regenerative medicine to schizophrenia and ASD. ZIRC relieves scientists from having to maintain the zebrafish lines they have generated in their own laboratories, which on a small scale can be resource intensive, prevent duplication of efforts, and ensure research rigor and reproducibility.

Genomic studies, as part of the PMI, have revealed mutations of many genes associated with human diseases. However, the functions of these genes and their potential as drug targets are not well understood. Researchers supported by ORIP have generated many transgenic *Drosophila* (fruit fly) stocks carrying known modifications of genes associated with human diseases.[2273,2274] Researchers are using these fruit fly models of human disease to understand gene function for complex genetic diseases—including aortic aneurysm, DiGeorge syndrome, and infantile cataracts—and to develop diagnostic and therapeutic approaches.[2275– 2279]

[2271] https://orip.nih.gov/about-orip/research-highlights/go-resource-center-zebrafish-researchers.
[2272] https://zebrafish.org/home/guide.php.
[2273] http://labs.icahn.mssm.edu/rosscaganlab/.
[2274] http://flypush.imgen.bcm.tmc.edu/lab/index.html.
[2275] Sonoshita A, et al. *Nat Chem Biol* 2018;14(3):291-8. PMID: 29355849.
[2276] Schlessinger A, et al. *Cell Chem Biol* 2017;24(12):1434-5. PMID: 29272700.
[2277] Tan KL, et al. *Dev Cell* 2018;45(2):226-44. PMID: 29689197.
[2278] Liu N, et al. *Hum Mol Genet* 2018;27(14):2454-65. PMID: 29726930.
[2279] Ansar M, et al. *Am J Hum Genet* 2018;103(4):568-78. PMID: 30290152.

Figure 131. A postdoctoral lab mentor and a student in the High School Scientific Training and Enrichment Program check on the results of their fruit fly genetics experiment. Credit: Office of Intramural Training and Education, NIH.

Research Centers, Networks, and Consortia

NIH participates in or funds many different consortia, clinical trial programs, networks, and research collaborations that help to move science forward by supporting interdisciplinary teams. As opposed to multidisciplinary research, which involves teams of scientists approaching a problem from their own discipline, interdisciplinary research integrates elements of a wide range of disciplines—often including basic research, clinical research, behavioral biology, and social sciences—so that all the scientists approach the problem in a new way. Members of interdisciplinary teams learn from one other to produce new approaches to a problem that would not be possible through any one of the individual disciplines.

Research centers, networks, and consortia catalyze scientific advancement by taking advantage of the power of collaboration and the sharing of information, resources, and infrastructure for advancing the development of high-priority areas. For example, in FY 2016, NHGRI launched the Centers for Common Disease Genomics (CCDG) to conduct in-depth genomics studies of nine complex and common cardiovascular, neuropsychiatric, and immune-mediated diseases.[2280] The causes of these diseases can be difficult to decipher because they result from a complex combination of genomic influences and environmental factors. Today the CCDGs have generated genome sequences from more than 100,000 people and are using the data generated to uncover genomic variants that increase the risk for these common diseases.

[2280] https://www.genome.gov/27563570/centers-for-common-disease-genomics-ccdg/.

Figure 132. The Centers for Common Disease Genomics will use genome sequencing to explore the genomic contributions to common diseases that affect hundreds of millions of people worldwide. Credit: Ernesto del Aguila III, NHGRI.

NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of research. To that end, ORIP's National Primate Research Centers Program facilitates and contributes to basic science and translational biomedical research by providing facilities, animals for research, and expertise in all aspects of nonhuman primate biology and husbandry. For example, as part of efforts to develop contraceptive options for men, a small organic compound, EP055, that targets a protein on the surface of sperm and inhibits motility in vitro was tested in male monkeys at the Oregon National Primate Research Center.[2281] After intravenous infusion of a single high dose of EP055, sperm motility was transiently suppressed, demonstrating its potential as a reversible male contraceptive.[2282]

Transplantation is often the preferred or only therapy for end-stage organ disease, yet the number of patients on waiting lists greatly exceeds the number of available organs. In 2018, more than 114,000 patients were on the Organ Procurement and Transplantation Network waiting lists, but approximately 34,000 organ transplants were performed in the U.S. To help solve this problem, scientists want to use organs from other species, such as the pig. Cross-species transplantation, or xenotransplantation, offers a potential interim or definitive solution to the severe shortage of human organs for transplantation. However, one major obstacle to successful xenotransplantation is a strong immune system response by the organ recipient, which can lead to organ rejection and failure, as well as public health concerns regarding the potential for cross-species infection with viruses and other potentially new or unidentifiable infectious agents. To overcome these challenges, the National Swine Resource and Research Center has been engaged with the research community and its NIH ICO partners—ORIP, NHLBI, and NIAID—to meet xenotransplantation resource infrastructure needs by exploring a variety of strategies to prevent or minimize rejection and cross-species infection.[2283] Approaches have included using state-of-the-art

[2281] https://www.nih.gov/news-events/nih-research-matters/experimental-male-contraceptive-blocks-sperm-movement.
[2282] O'Rand MD, et al. *PLoS One* 2018;13(4):e0195953. PMID: 29672554.
[2283] https://nsrrc.missouri.edu/.

genome editing strategies to develop and enhance pig model systems for xenotransplantation, including severe combined immunodeficiency pig models.[2284– 2289]

To assist those interested in including -omics in their program of nursing research, NCI, NHGRI, and NINR have created a new web-based resource called the Omics Nursing Science and Education Network (ONSEN). The goal of ONSEN is to facilitate investigator-driven research through the creation of a web-based collaborative research network infrastructure that will provide information, resources, and networking opportunities. Initiated from the nursing genomics community, the website includes a searchable database of -omics projects and aims to foster collaborations among investigators in all disciplines.[2290] The website also provides opportunities to identify mentors and pre- and postdoctoral opportunities in -omics research.

NIA supports 12 research networks to provide infrastructure for advancing the development of high-priority areas of behavioral and social research relevant to aging. NIA renewed support for "High-Priority Behavioral and Social Research Networks," which aim to produce resources that will serve the field at large.[2291] In addition, NIA released a new announcement, *High-Priority Behavioral and Social Research Networks in AD/ADRD*, designed to address the network development needs of researchers interested in advancing transdisciplinary AD/ADRD-relevant research agendas in the social and behavioral sciences.[2292]

To establish a national multidisciplinary laboratory, NCATS launched the CTSA program Trial Innovation Network (TIN) as a collaboration among three key partners: (1) three Trial Innovation Centers, (2) one Recruitment Innovation Center (RIC), and (3) the CTSA program hubs.[2293] The long-term goal is to discover ways to accelerate and improve multicenter clinical trials and studies that answer meaningful clinical questions and inform clinical care.[2294] The TIN aims to achieve this mission by testing new methods to improve the clinical trials process, building quality into the design of protocols, streamlining IRB and contracting processes, incorporating novel approaches to project management, and using data-driven approaches to evaluate and optimize clinical trials at every point—from protocol design to the publication of results. The CTSA program RIC, a component of the TIN, leverages expertise in clinical informatics and patient and community engagement to increase the number of underrepresented persons included in

[2284] https://orip.nih.gov/about-orip/research-highlights/severe-combined-immunodeficient-pigs-promising-model-human-stem-cell.
[2285] Lee W, et al. *Cornea* 2016;35(1):105-13. PMID: 26418433.
[2286] Scott PA, et al. *Transl Vis Sci Technol* 2017; 6(2):4. PMID: 28316877.
[2287] Yuan Y, et al. *Proc Natl Acad Sci U.S.A.* 2017;114(29):E5796-804. PMID: 28673989.
[2288] Boettcher AN, et al. *Front Oncol* 2018;8:559. PMID: 30560086.
[2289] Powell EJ, et al. *Lab Anim* 2018;52(4):402-12. PMID: 29325489.
[2290] https://omicsnursingnetwork.net/.
[2291] https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-015.html.
[2292] https://grants.nih.gov/grants/guide/rfa-files/rfa-ag-19-016.html.
[2293] https://trialinnovationnetwork.org/.
[2294] https://ncats.nih.gov/ctsa/projects/network.

clinical research studies. To date, the RIC has provided more than 60 consultations to investigators seeking assistance with their clinical trial.[2295]

To help guide regenerative medicine therapies through preclinical studies and into human clinical trials, NIDCR established the Dental, Oral, and Craniofacial Tissue Regeneration Consortium.[2296] In 2016, Stage 1, a one-year planning phase, was successfully completed. The first two phases of this initiative created multidisciplinary research teams comprising scientists, clinicians, industry partners, regulatory agencies, and commercialization experts who worked on more than a dozen interdisciplinary translational projects at two research centers.[2297] In one such effort, scientists are creating a safe and effective device for reconstructing temporomandibular joint discs; in another, researchers are advancing a treatment for periodontal disease that blocks the protein sclerostin, which impedes bone growth.[2298]

Sometimes collaboration is inspired by a new and exciting technology, such as cryo-EM, a Nobel Prize–winning imaging method that provides more accurate models of molecular structure and a greater understanding of biological function. In FY 2018, NIH, through the NIH Common Fund and NIGMS, launched the Transformative High-Resolution Cryo-Electron Microscopy program to fund three service centers.[2299,2300] These centers are equipped with state-of-the-art equipment and cross-training capabilities for the production and analysis of high-resolution data that provide detailed information about viruses, proteins, and other medically important biomolecules. In addition to the three national service centers, this program supports the development of training materials to build a skilled and technically savvy cryo-EM workforce.

In response to NIH's new Clinical Trials policies, OBSSR and OSP collaborated to develop a protocol template to help behavioral and social science researchers prepare research protocols for human studies measuring a social or behavioral outcome or testing a behavioral or social science–based intervention.[2301] The template is fully integrated into NIH's existing Clinical Electronic Protocol Writing Tool, allowing researchers to easily create protocol documents ready for submission to *ClinicalTrials.gov* or the NIH IC funding the research. Use of the protocol will enhance rigor and reproducibility and allow the NIH to collect, track, and report NIH-funded clinical trials.

Capacity Building

Building research capacity and infrastructure is the foundation for advancing research in human health and disease and is crucial for fostering discoveries that can ultimately be translated into clinical practice. NIH's approach to capacity building includes such activities as developing research methods and

[2295] Selker HP, et al. *Clin Pharamcol Ther* 2019;105(4):857-66. PMID: 30610746.
[2296] https://www.nidcr.nih.gov/news-events/nidcr-news/2017/nidcr-funds-consortium.
[2297] https://doctrc.pitt.edu/.
[2298] http://c-doctor.org/.
[2299] https://www.commonfund.nih.gov/CryoEM.
[2300] https://www.nih.gov/news-events/news-releases/nih-funds-three-national-cryo-em-service-centers-training-new-microscopists.
[2301] https://obssr.od.nih.gov/the-behavioral-and-social-clinical-trials-template-a-new-resource/.

streamlined protocols and procedures, improving research infrastructure and facilities, developing tools and resources to help researchers, promoting scientific collaborations, and preparing for future research opportunities.

Through its CTSA program, NCATS developed a single IRB platform for multisite clinical studies, called the NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform. The goal of the SMART IRB Platform is to provide flexible resources that researchers nationwide can use to harmonize and streamline IRB review for their own multisite studies, thereby enhancing the speed and efficiency of the IRB review process for conducting clinical trials.[2302,2303] The SMART IRB Platform is designed to ease common challenges associated with initiating multisite research and to provide a roadmap for institutions to implement the NIH Single IRB Review policy. As of November 2018, SMART IRB signatories had reached a total of 500 institutions across the U.S., including CTSA hubs and their affiliates and collaborators, along with other institutional and organizational entities involved in human-subject research. NCATS continues to support the further dissemination of the SMART IRB Reliance System on a national basis through educational resources and outreach, implementation assistance, and development of a plan to ensure the future sustainability of the SMART IRB Reliance System.

Research frameworks are one example of a streamlined protocol and procedure for capacity building. To this end, NIEHS developed a comprehensive translational research framework to provide a clear concept for researchers to plan, understand, evaluate, and communicate environmental health research.[2304] The framework also enables researchers to move their research ideas across multiple translational areas.

To improve research infrastructure and facilities, NIEHS announced a FOA to support the maintenance of existing environmental epidemiology cohorts and to enrich the infrastructure needed to prepare for future research opportunities through resource sharing and broader scientific collaborations.[2305]

NICHD's Population Dynamics Research Infrastructure Program aims to advance the field of population dynamics research, which supports data collection and research on human health, productivity, behavior, and development at the population level, using such methods as inferential statistics, natural experiments, policy experiments, statistical modeling, and gene–environment interaction studies.[2306] The primary objectives of the Infrastructure program are to increase the scientific impact, innovation, and productivity of population dynamics research; increase competitiveness for peer-reviewed external funding in population dynamics research; support career development experiences for junior population dynamics scientists that will contribute to their research independence; and maximize the efficiency of funding for population dynamics research by minimizing the financial and time burdens of providing administrative and other support services associated with research projects. The program is also designed

[2302] https://ncats.nih.gov/ctsa/projects/smartirb.
[2303] https://smartirb.org/.
[2304] https://www.niehs.nih.gov/research/programs/translational/framework-details/index.cfm.
[2305] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-18-009.html.
[2306] https://www.nichd.nih.gov/research/supported/PDRIP.

to support the broad dissemination of data, methods, and materials in the field of population dynamics research.

To build capacity in NIH's peer review process, the Prevention Research Expertise Survey was developed by ODP to build a directory of experts in prevention research methods and study designs.[2307] The directory will help Scientific Review Officers at CSR identify researchers with expertise in specific prevention science methods and content areas and invite them to serve on NIH review panels. Their participation will help strengthen the panels and improve the quality of prevention research supported by the NIH. In addition, ODP developed and released the Resources for Researchers component of its website, which includes a searchable library of federal tools and resources to help investigators develop and conduct prevention research projects.[2308]

In FY 2018, NIGMS started the STTR Regional Technology Transfer Accelerator Hubs for IDeA States Initiative to promote entrepreneurship, technology transfer, management, small business finance, and other skills needed to move discoveries and technologies out of the laboratory into commercial products that address human health.[2309,2310] Four new grant awards were made, each supporting one shared STTR Accelerator Hub in one of the four IDeA regions (Central, Northeastern, Southeastern, and Western).[2311] These hubs will provide infrastructure and expertise and produce educational tools (e.g., curricula, texts, webinars) to accelerate technology transfer, build an entrepreneurial culture at IDeA institutions, and produce more successful SBIR and STTR applications.

In addition, the IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR) initiative develops network infrastructure and capacity in eligible states to conduct clinical and translational research focused on health concerns that affect medically underserved populations or that are prevalent in IDeA states. The IDeA-CTR awards support mentoring and career development activities in clinical and translational research. NIGMS supported four new IDeA-CTR awards in FY 2016, one in FY 2017, and one in FY 2018. Currently, 11 IDeA-CTR awards are active. In FY 2018, the IDeA Program allocated $1 million to fund administrative supplements to existing IDeA-CTR awards for new pilot projects addressing the opioid epidemic in IDeA states.[2312] Four administrative supplement awards were made for the following projects: (1) a community survey to assess attitudes toward opioid addiction, prevention, and treatment services in rural West Virginia; (2) identification of modifiable biological, psychological, and social factors that underpin comorbid chronic low back pain and opioid addiction; (3) primary care use and health outcomes after intrauterine opioid exposure; and (4) profiling community drug abuse by analysis of municipal wastewater.

[2307] https://prevention.nih.gov/research-priorities/prevention-research-expertise-survey-pres.
[2308] https://prevention.nih.gov/research-priorities/resources-researchers#!/tool.
[2309] https://www.nigms.nih.gov/Research/mechanisms/Pages/STTR-Regional-Technology-Transfer.aspx.
[2310] https://grants.nih.gov/grants/guide/rfa-files/RFA-gm-18-001.html.
[2311] https://www.nih.gov/news-events/news-releases/nih-grants-will-spur-innovation-under-resourced-states.
[2312] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-18-027.html.

Websites and Workshops

Sharing knowledge, best practices, and information is critical to advancing science and improving lives, and NIH strongly supports opportunities for open science, transparency, identification of research gaps and areas for improvement, communication, and collaboration through its many websites and workshops. A few examples are illustrated here, with other examples included throughout this report.

In September 2016, NINR held a scientific symposium on *Advancing Science, Improving Lives: A Window to the Future*.[2313] This event brought together scientists, health care professionals, and members of the public to examine the advancements in nursing science that lay the foundation for clinical practice and enhance the health of the nation. The scientific symposium featured distinguished scientific speakers and included panel discussions on the topics of sleep and -omics science.

In 2017, ORWH hosted the *Sex as a Biological Variable Workshop* to highlight the scientific insights of select recipients who received supplemental funding through the NIH Common Fund and ORWH.[2314,2315] Researchers presented their scientific results and shared their challenges and approaches to the inclusion of SABV in research design, spanning the entire continuum from basic through translational to clinical research analyses and reporting.

Since 2016, OBSSR and the Behavioral and Social Sciences Research Coordinating Committee have been hosting an annual *NIH Behavioral and Social Sciences Research Festival*[2316] to inform the research community, stakeholders, and ICOs about the latest NIH-funded behavioral and social sciences research and its overall impact and importance across the entire field of biomedical research. Additional goals are to assist the ICOs with the establishment of research priorities and the coordination of their programmatic efforts, thus minimizing redundancy and maximizing returns on NIH investments in behavioral and social sciences research.

Finally, each year ODP hosts the Pathways to Prevention (P2P) program to identify research gaps in a selected scientific area, identify methodological and scientific weaknesses in that scientific area, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of a complex public health issue.[2317] P2P workshops are designed for topics that have incomplete or underdeveloped research and for which it is difficult to produce a report synthesizing published literature. ODP collaborates with various NIH ICOs, as well as other federal partners, to sponsor the workshops. Recent workshops have included the following topics: *Advancing Research to Prevent Youth Suicide* (2016), *Methods for Evaluating Natural Experiments in Obesity* (2017), and *Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention* (2018).

[2313] https://www.ninr.nih.gov/newsandinformation/newsandnotes/30th-concluding-video.
[2314] https://orwh.od.nih.gov/sites/orwh/files/docs/SABV_Workshop_RevisedFlyer_20171003_SR.pdf.
[2315] Pettibone KG, et al. *Environ Health Perspect* 2018;126(7):074501. PMID: 30024381.
[2316] https://obssr.od.nih.gov/wp-content/uploads/2018/03/OBSSR_Festival_Report_2017.pdf.
[2317] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention.

Chapter 4 Centers of Excellence

NIH Centers of Excellence programs are diverse in focus, scope, and origin. In general, they facilitate and coordinate research efforts on a specific disease, group of diseases, or area of research. Some were created as NIH-wide initiatives, others by individual ICs and Offices within the NIH OD; some reflect mergers or redesignations of existing programs; and some were mandated by Congress. The NIH Centers of Excellence programs described in this report are a subset—those established by statutory mandate.

Alzheimer's Disease Research Centers

Establishment of the Alzheimer's Disease Research Centers

Congressional as well as public interest has focused on research on the causes, diagnosis, treatment, and prevention of Alzheimer's disease (AD) and related dementias, as well as on disparities and cost and coordination of care. In 1984, Congress directed NIH, and in particular the NIA, to foster further research related to AD. The NIA Alzheimer's Disease Research Center (ADRC) program is authorized by the *PHS Act*, Section 445, and currently includes 31 NIA-designated ADRCs.

The first ADRCs were established through NIH funding in the mid-1980s in response to the directive, information on AD emerging from the work of NIH grantees and other researchers, and the prospect of a medical and social crisis triggered by an explosion of AD cases due to population aging. Although each center has its own emphasis, the program's principal objectives are to conduct cutting-edge basic, clinical, translational, and social/behavioral research; to train the next generation of researchers; and, very important, to provide information to the public about research findings, access to support services, and opportunities to participate in research. Much of the research takes place through multicenter cooperative studies designed to better understand the causes and effects of AD and to develop and test new interventions for the diagnosis, treatment, and prevention of AD and other age-related neurodegenerative diseases.

How the ADRCs Function Within the NIH Framework

NIH currently funds 31 ADRCs, as well as the National Alzheimer's Coordinating Center (NACC), which coordinates data collection and fosters collaborative research among ADRCs (Table 1). Funding for the ADRCs comes from NIA through P30 center core grant mechanisms. Each center is funded for 5 years, and ADRCs compete through a peer review process for additional funding. New applicants for ADRC funding compete with existing grantees.

Description of Disease or Condition

AD is the most common form of dementia among older people. It is an age-related, irreversible brain disorder that develops over many years. In the earliest stage, people experience memory loss or other behavioral or cognitive changes, which are usually mild and sometimes mistaken for changes that may occur during the normal aging process. As the disease progresses, however, these symptoms gradually lead to dementia, a condition characterized by marked memory loss accompanied by behavior and personality changes. The disease also leads to a decline in other cognitive abilities (such as decision-making and language skills) and eventually to an inability to recognize family and friends and to severe mental decline. We are understanding more and more that the observed symptoms are most likely related to more than one underlying biological cause.

The most important known risk factors for the development of AD are age and family history, although education, diet, and environment appear to play a role. Scientists are finding that some of the risk factors for heart disease and stroke—such as high blood pressure, high cholesterol, and low levels of the vitamin folate—are also associated with an increased risk for AD. Evidence from observational studies suggests that physical, mental, and social activities may help delay the onset of AD, and clinical trials are beginning to bear this out, although the exact mechanisms are still unknown. Considerable progress has been made in recent years and—with the additional funding the field has received leading to better understanding the mechanisms, risk factors, and opportunities for intervention—hope for a treatment is increasing.

Burden of Illness

More than 5 million Americans age 65 or older are estimated to be living with Alzheimer's disease, the most common form of dementia.[2318] Many others have an AD-related form of dementia. Experts agree that these numbers will increase significantly if current U.S. demographic trends continue and no effective prevention or treatment methods emerge. Recently, several large studies suggested that dementia rates in the U.S. and parts of Europe may be declining, at least for now, possibly due to such factors as improved education and treatment of risk factors for stroke and heart attack. That said, the greatest risk factor for Alzheimer's is age—the number of people with the disease doubles for every 5-year interval beyond age 65—and the American population is indisputably aging. The U.S. Census Bureau estimates that the size of the population age 65 and older will increase to about 72 million people in the next 25 years. Moreover, the fastest growing segment of the U.S. population consists of people age 85 years or older.

Economic costs of the disease are also considerable: Investigators in one recent NIA-supported study found that in the last 5 years of life, total health care spending for people with dementia was more than $250,000 per person, 57 percent greater than costs associated with death from other diseases, including cancer and heart disease.[2319] A separate NIA-supported analysis calculated that the cost of caring for people over age 70 with dementia in the U.S. was between $159 billion and $215 billion in 2010—

[2318] Hebert LE, et al. *Neurology* 2013; 80(19), 1778-83. PMID: 23390181.
[2319] Kelley AS, et al. *Ann Intern Med* 2015;163(10):729-36. PMID: 26502320.

comparable to, if not greater than, costs of care for heart disease and cancer. Dementia-related costs are expected to rise dramatically in the coming decades as the baby boom generation ages.

Scope of NIH Activities: Research and Programmatic

Although research on AD has long been a cornerstone of NIA's research portfolio, NIH's efforts against AD entered a new and significantly expanded phase in 2011 with the passage of the *National Alzheimer's Project Act (NAPA)*.[2320] The law renewed and strengthened national efforts to find effective treatments for AD and to support people with dementia and their caregivers. As a result, in 2012 the *National Plan to Address Alzheimer's Disease* outlined objectives and set milestones toward achieving these goals. Updated annually, the plan is a collaborative and constantly reevaluated framework that helps focus efforts to provide better clinical care and improve services for people with the disease and their families.[2321] NIH progress toward achieving *NAPA* research milestones is tracked and reported through periodic review of the research funded, results achieved, and new initiatives and programs begun.

Further momentum against AD developed in 2015 with the creation of the first NIH Bypass Budget for Alzheimer's and Related Dementias (presenting a budget for FY 2017). The Bypass Budget was developed in response to language in the FY 2015 *Appropriations Act* requiring "an annual budget estimate (including an estimate of the number and type of personnel needs for the Institutes) for the initiatives of the NIH pursuant to the *National Alzheimer's Plan*" to be submitted to the President on an annual basis. Strategic planning efforts informing the annual development of this budget include the following:

- 2012, 2015, and 2018 Alzheimer's Disease Research Summits
- 2013, 2016, and 2019 conferences on Alzheimer's Disease-Related Dementias
- 2017 Alzheimer's Care and Services Summit (a 2020 Summit is planned)
- A 2013 meeting on Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome, a uniquely vulnerable population

The ADRC program supports the goals outlined in the *NAPA* plan and the Bypass Budget, providing infrastructure and core resources to enhance ongoing research by bringing together basic biomedical, behavioral, social, and clinical scientists to study the causes, progression, prevention, diagnosis, and treatment of AD and to improve health care delivery. In addition, the network provides an infrastructure to facilitate NIA signature programs such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Alzheimer's Clinical Trials Consortium (ACTC).[2322] ADRCs also foster the development of new research approaches and provide training opportunities for research fellows and junior faculty interested in conducting interdisciplinary AD research.

[2320] http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf.
[2321] http://aspe.hhs.gov/2014-national-alzheimers-disease -plan-available.
[2322] https://www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc.

In 2017, NIA—in partnership with leading experts from academia, industry, and the nonprofit world—completed a strategic planning process that resulted in a set of 166 recommendations[2323] to guide the ADRCs in supporting the integrated translational research agenda that emerged from the various Summits and is outlined in the National Plan's research implementation milestones. These recommendations address all aspects of the ADRC program, including clinical research capacities, maximizing the value of the unique neuropathological expertise across the ADRCs, translational research, interactions and networking, infrastructural support, and training. NIA is currently in the process of reviewing each recommendation, engaging various groups to propose and lead the required steps to complete each, and tracking progress on successful completion of the goals outlined in the recommendations.

Resources shared among ADRCs include data (through the NACC), biological samples (through the National Centralized Repository for Alzheimer's Disease and Related Dementias [NCRAD]), and genetic information (through the Alzheimer's Disease Genetics Consortium [ADGC]).

Notably, NCRAD, hosted by Indiana University, collects and shares blood, DNA, and cell lines with qualified researchers. The repository recently received substantial additional funding to increase the number and types of samples being collected. NCRAD works directly with the NIH Alzheimer's Disease Genetics Initiative, which was established to identify genetic risk factors for late-onset AD, and ADGC, which conducts large-scale whole-genome studies on AD. ADGC itself maintains one of the largest collections of samples available for GWAS of AD, which are being used to identify the susceptible and protective genes influencing the onset and progression of late-onset disease. These samples are especially valuable because of the rich associated clinical data available for each participant. In 2011, ADGC was one of four groups that established the International Genetics of Alzheimer's Project, a multinational collaboration to identify and map genes that contribute to the disease.

The ADRCs have helped create additional collaborative research resources and projects, including the NACC, ADNI, and ACTC. Descriptions of these and other efforts are provided in the following section.

Much of the important progress in AD research in the U.S. during the past 35 years stems from research conducted at or resources provided by the ADRCs. ADRC scientists have conducted a significant amount of the research on protein processing related to plaque and tangle formation in the brain, hallmarks of AD. ADRC researchers have also identified the common properties of the abnormal proteins associated with several neurodegenerative diseases. In recent years, ADRC researchers have evaluated cognitive changes associated with normal aging and the transitions to mild cognitive impairment (early difficulties with thinking and remembering) and dementia. With that research has come a more precise understanding of the timing of various types of cognitive change, as well as the development of better ways to measure and evaluate those changes. ADRC researchers have also identified factors that contribute to changes in cognitive abilities, such as social and physical activity.

[2323] https://www.nia.nih.gov/news/expert-panel-offers-transformative-recommendations-nih-alzheimers-research-centers.

Currently, many ADRCs are carrying out important studies relating changes in brain structure to the clinical stages of AD. For these studies, researchers are examining patients enrolled in the clinical cores, brain imaging supported by imaging cores, and autopsy evaluations from the neuropathology cores. ADRC researchers are also examining relationships and commonalities between AD and cerebrovascular disease or other neurodegenerative diseases, as well as contributions by coexisting non-neurological conditions that occur in people with AD. In addition, the ADRCs are exploring commonalities between AD and other dementias, including Parkinson's disease dementia; collaborations are underway with the NINDS-supported Morris K. Udall Centers of Excellence for Parkinson's Disease to examine many overlapping scientific and clinical issues.

Another major objective for the ADRCs is to recruit racially and ethnically diverse research participants for AD research. Different centers have different special population foci, including African American, Hispanic, Native American, and Asian American participants. NACC data now show that approximately 20 percent of people enrolled in the ADRCs are non-White.

All ADRCs have Outreach, Recruitment, and Education Cores (ORECs) that provide outreach to the public and facilitate participant recruitment for large-scale national projects, such as NIA's Genetics Initiative, ACTC, and ADNI. Collaborations include ongoing interactions with such organizations as the Alzheimer's Association, the HHS Administration on Aging, and NIH's Alzheimer's Disease Education and Referral Center. The ADRCs pay special attention to issues of cultural sensitivity and, where appropriate, structure information to effectively reach diverse populations, including people for whom English is not a first language.

In 2019, NIA unveiled the Alzheimer's and Dementia Outreach, Recruitment, and Engagement Resources (ADORE) website,[2324] a repository of materials submitted by ADRCs and other organizations to support recruitment and retention of participants into clinical trials and studies. ADORE includes recruitment plans, videos, articles, toolkits, and more. The centers' unique expertise was also instrumental in the development of the National Strategy for Recruitment in Participation in Alzheimer's and Related Dementias Clinical Research,[2325] which was released in October 2018.

NIH Funding for FY 2016, FY 2017, and FY 2018

NIH funding for the ADRCs was $62.38 million in FY 2016, $62.97 million in FY 2017, and $68.69 million in FY 2018.

[2324] https://www.nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources.
[2325] https://www.nia.nih.gov/research/recruitment-strategy.

FY 2016, FY 2017, and FY 2018 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments for the ADRCs include the following examples:

National Alzheimer's Coordinating Center (NACC)

In 1999, NIH established NACC to facilitate collaborative research and standardize procedures among the ADRCs. NACC developed and maintains a large database of standardized clinical and neuropathological research data collected from each ADRC. This database is a valuable resource for both exploratory and explanatory AD research. The data provided by the NACC support large studies that use patient samples from ethnically, racially, and geographically diverse populations and multiple ADRCs. A minimum data set of 67 variables collected from the ADRCs contains data on more than 74,000 people enrolled since 1984. A much richer longitudinal Uniform Data Set (comprising 725 variables) has been collected from more than 40,000 participants enrolled since 2005. NACC itself has funded 24 collaborative multicenter studies, 21 junior investigator awards to use NACC data, and 6 new investigator awards to promote young investigator development; more than 850 publications utilizing NACC data have been published to date. Currently NACC is averaging 40 data requests per month from both national and international investigators

In 2013, NACC began accepting voluntary contributions of brain images from ADRCs. More than 7,000 images on over 5,200 subjects, including those of participants from underrepresented groups, are now included in the database. These images are linked with the Uniform Data Set already collected on all participants and can now be linked to the genotype data from ADGC (when the data are available and appropriate consent has been obtained). Further information is available on the NACC website.

Today, the NACC database is one of the largest and most comprehensive databases of its type in the world. Data collected by NACC are freely available for all scientists to use in research studies through the Global Alzheimer's Association Interactive Network, a gateway that allows researchers around the world to obtain access to a vast collection of AD research data, sophisticated analytical tools, and computational resources.

Alzheimer's Clinical Trials Consortium (ACTC)

The ACTC, an infrastructure of 35 sites across the U.S., was established in 2017 to accelerate and expand studies for therapies in AD and related dementias. The ACTC is anticipated to address the time frame, complexity, and expense of the recruitment process and site activation for Alzheimer's trials to find new and effective ways to treat or prevent these devastating disorders. It will also provide needed clinical trial infrastructure in such areas as imaging, biostatistics, and data management. As part of its recruitment efforts, the ACTC has established a new Minority Outreach and Recruitment Team, which will use innovations in recruitment to support both central and local partnerships with diverse communities.

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Nearly all ADRCs participate in ADNI, an innovative public–private partnership that is examining the potential of serial MRI, PET, and tests of other biomarkers to measure the development and progression of mild cognitive impairment and AD earlier and with greater sensitivity.

ADNI was established in 2004 and is now in its third phase, ADNI3. ADNI3 began in 2016 with an expanded goal of determining the relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics across the entire spectrum of AD. ADNI3 adds brain scans that detect tau protein tangles, a key indicator of the disease. This phase also continues the discovery, optimization, standardization, and validation of clinical trial measures and biomarkers used in AD research.

Research Activities and Outcomes

Since the establishment of the ADRC program in 1984, investigators have published thousands of research papers on all aspects of AD and related disorders. A recent analysis identified more than 12,000 scientific papers based on ADRC research.[2326] Topics have ranged from the disease's biology to its family and societal impact, as well as many studies of diagnosis and treatment. In addition, the ADRC program has demonstrated tremendous success in facilitating collaborations across institutions, and collaborative multi-ADRC research articles are consistently cited more frequently than AD articles overall.

Research accomplishments include the following important studies performed by ADRC scientists, highlighting research carried out by several centers. These are only a few examples from a wide range of research studies conducted by the ADRCs, and they demonstrate the breadth of research the ADRCs support:

- **Identification of Blood Biomarkers for AD.** Investigators at the Washington University in St. Louis ADRC have made an important step forward in the development of a viable method for measuring amyloid in the blood. The new method for measuring plasma Aβ, which relies on mass spectrometry, greatly increases accuracy and precision over previous antibody-based measures. The initial findings have been replicated in an independent cohort, but the method requires validation in multicenter studies and clinical settings. However, because this method costs about a tenth of the price of an amyloid PET scan—and is also less time-consuming and burdensome to the patient—if it is validated, it may significantly lower the costs and greatly facilitate screening potential participants for clinical trials.[2327]
- **Sex Differences in AD/ADRD.** Sex as a biological variable in the etiology of dementia and Alzheimer's disease is a topic of interest to many of the centers. For example, investigators from several centers used ADNI data in conjunction with diverse medical, clinical, and genetic factors to perform a sex-stratified analysis of cognitive impairment. The analysis, which was unprecedented in scale and scope, applied sophisticated informatics approaches to three large

[2326] Hughes ME, et al. *JAMA Neurol* 2014;714:412-20. PMID: 24514750.
[2327] Ovod V, et al. *Alzheimer's and Dementia* 2017;13:841-9, 2017. PMID: 28734653.

Alzheimer's databases. Analyses suggested females were 1.5 times more likely than males to have a documented diagnosis of probable Alzheimer's disease, and several other factors fell along sex-specific lines and were possibly associated with severity of cognitive impairment.[2328] Elsewhere, centers investigators performed sex-stratified analyses of postmortem tissue using established biomarkers and identified sex differences in the expression of genes involved in both amyloid and tau pathologies.[2329] Elsewhere, center investigators found that contrary to long-standing views, men and women with the APOE ε3/ε4 genotype (associated with an increased risk of late-onset disease) have nearly the same odds of developing AD from age 55 to 85 years, but women have an increased risk at younger ages.[2330]

- **CVD and Alzheimer's: A Genetic Link?** Cardiovascular- and lifestyle-associated risk factors are increasingly recognized as important for Alzheimer's disease pathogenesis. Beyond the ε4 allele of apolipoprotein E (APOE), which is known to be involved in lipid transport, comparatively little is known about whether cardiovascular-associated genes also increase risk for AD. ADRC investigators were part of a multinational team using GWAS to identify genetic alterations that are jointly associated with AD and cardiovascular risk factors (e.g., body mass index, type 2 diabetes, coronary artery disease, waist–hip ratio, and cholesterol markers). They found that certain alterations associated with plasma lipids are also associated with AD. These findings support previous work suggesting that lipid biology is integral to the development of AD.[2331]
- **Do Proton Pump Inhibitors Increase Dementia Risk?** Results of some studies have suggested that use of proton pump inhibitors (PPIs)—a class of drugs frequently prescribed to treat gastrointestinal disorders, such as duodenal ulcers and gastroesophageal reflux disease—may be associated with increased risk of mild cognitive impairment and Alzheimer's disease. ADRC investigators used longitudinal data from the NACC database, collected over 10 years (2005–2015), to explore a possible association between self-reported PPI use and mild cognitive impairment and Alzheimer's. They found that PPI use was not associated with greater risk of dementia or AD among study participants. These findings are reassuring to older individuals who take a PPI for gastrointestinal symptoms; however, further study is needed to definitively determine the impact of PPIs on cognition.[2332]

Recommendations for Improving ADRCs' Effectiveness, Efficiency, and Outcomes

Evaluation Plans

The National Advisory Council on Aging (NACA) evaluates and makes recommendations for the ADRC program. The most recent evaluation took place in 2017 and produced a comprehensive report recommending strategic revisions to the ADRC program that will enable it to achieve NAPA objectives by

[2328] Ronquillo JG, et al. *J Women Aging* 2016;28(5):403-11. PMID: 57105335.
[2329] Deming Y, et al. *Acta Neuropathol* 2018;136:857-72. PMID: 29967939.
[2330] Neu SC, et al. *JAMA Neurol* 2017;74:1178-89. PMID: 28846757.
[2331] Broce IJ, et al. *Acta Neuropath* 2019;137:209-26. PMID: 30413934.
[2332] Goldstein FC, et al. *J Am Geriatr Soc* 2017;65:1969-74.

leveraging resources, capabilities, and research participants across the network.[2333] The next evaluation is scheduled for 2027. More broadly, NACA reviews the NIA Division of Neuroscience, in which the ADRC program is housed, every 4 years. The most recent review was in January 2019.

Future Directions

NIH plans to have the ADRCs continue to emphasize research related to the transition from normal aging to mild cognitive impairment and to full-blown AD, as well as studies of the overlap between AD and other neurodegenerative diseases. Because recent studies, including ADRC studies, have suggested that disease processes common to a number of conditions may overlap in people with symptoms of dementia,[2334] a particular focus will be on the etiology, diagnosis, and treatment of mixed dementias. In addition, the ADRCs will continue to search for biomarkers that predict cognitive decline and diagnose cognitive impairment and dementia. Identifying and addressing disparities among populations will also continue to be a priority.

Table 1. ADRCs

Institution and Location	Year Established
University of California, San Diego, CA	1984
Massachusetts General Hospital, Boston, MA	1984
Mount Sinai School of Medicine, New York, NY	1984
University of Southern California, Los Angeles, CA	1984
Johns Hopkins University, Baltimore, MD	1984
University of Kentucky, Lexington, KY	1985
University of Pittsburgh, Pittsburgh, PA	1985
University of Washington, Seattle, WA	1985
Washington University in St. Louis, St. Louis, MO	1985
The University of Texas Southwestern Medical Center, Dallas, TX	1988
Columbia University Health Sciences, New York, NY	1989
Oregon Health & Science University, Portland, OR	1990
New York University School of Medicine, New York, NY	1990
Mayo Clinic College of Medicine, Rochester, MN, and Jacksonville, FL	1990
University of Pennsylvania, Philadelphia, PA	1991

[2333] See https://www.nia.nih.gov/sites/default/files/2017-06/ADC%20PANEL%20RECOMMENDATIONS%20FINAL%20June%202017.pdf.
[2334] Boyle PA, et al. *Ann Neurol* 2017;83(1):74-83. PMID: 29244218.

Institution and Location	Year Established
University of California, Davis School of Medicine, Sacramento, CA	1991
Indiana University, Indianapolis, IN	1991
Rush University Medical Center, Chicago, IL	1991
Boston University Medical Campus, Boston, MA	1996
Northwestern University, Chicago, IL	1996
University of California, Irvine, CA	2000
Arizona Alzheimer's Center, Phoenix, AZ	2001
University of California, San Francisco, CA	2004
Emory University, Atlanta, GA	2005
University of Wisconsin, Madison, WI	2009
University of Kansas Medical Center, Kansas City, KS	2011
Stanford University, Stanford, CA	2015
Yale University, New Haven, CT	2015
University of Florida, Gainesville, FL	2015
University of Michigan, Ann Arbor, MI	2016
Wake Forest University, Winston-Salem, NC	2016

Claude D. Pepper Older Americans Independence Centers

Establishment of the Claude D. Pepper Older Americans Independence Centers

In 1955, the U.S. Surgeon General established five Geriatric Research and Training Centers to advance research on the health care problems of the elderly and to train future academic leaders in the field of geriatrics. In 1989, Congress passed legislation that redesignated these Geriatric Research and Training Centers as the Claude D. Pepper Older Americans Independence Centers (OAICs), honoring efforts of the former Florida senator and representative to promote older Americans' health and well-being. Section 445A of the *PHS Act* (42 U.S.C. 285e-3) authorizes the OAICs to increase scientific knowledge leading to better ways to maintain or restore independence in older adults.

How OAICs Function Within the NIH Framework

NIH funding for the OAICs comes from NIA through a center grant mechanism (P30). The ultimate goal of the OAIC program is to translate research on aging to applications and interventions that increase or maintain independence for older people. NIH currently supports 14 OAICs (Table 2).

As Centers of Excellence in geriatrics research and training, the OAICs provide intellectual leadership in geriatrics research, encouraging and facilitating multidisciplinary and interdisciplinary collaborations in basic, translational, and clinical research relevant to older people's health and independence. In addition, each OAIC includes a Research Education Component to provide research training and career development opportunities in geriatrics and related fields.

Description of Disease or Condition

Age is a primary risk factor for many disabling diseases and conditions. However, human aging is a highly variable process; no single disease or condition is synonymous with aging. Understanding the process of aging is necessary to promote the health and well-being of older adults. Research in aging focuses on a range of conditions, including geriatric syndromes (e.g., low muscle mass/strength, mobility disability, urinary incontinence) and diseases and disorders that are more common among older adults, such as cancer, cardiovascular disorders, stroke, and sensory impairment.

Burden of Illness

Currently, nearly 56 million Americans are 65 years of age or older; of these, more than 6 million are 85 and older, and more than 80,000 have reached 100. By 2030, the number of individuals age 65 or older is likely to reach 73 million. The number of the oldest old, people age 85 or older, is expected to grow to over 18 million by 2050.[2335]

Older Americans use more health care than any other age group. As life expectancy increases, the health care system will need to find new ways to address disease and disability during later life.

Scope of NIH Activities: Research and Programmatic

OAICs are designed to develop or strengthen each awardee institution's programs in a key area of aging research, contribute to scientific understanding promoting greater independence for older people, and offer opportunities for training and career development for young scientists working in aging research. The program's ultimate goal is to enhance translation of basic and clinical research on aging into applications and interventions that increase or maintain independence for older people. The program also works to meet several contributing goals:

[2335] Projected Age Groups and Sex Composition of the Population: Main Projections Series for the United States, 2017–2060. U.S. Census Bureau, Population Division: Washington, DC. Revised September 2018.

- Provide intellectual leadership and innovation.
- Facilitate and develop novel multidisciplinary and interdisciplinary research strategies.
- Stimulate incorporation of emerging technologies, methods, and scientific advances into research designs as appropriate.
- Provide research career development for future leaders in geriatric research.
- Stimulate translation between basic and clinical research (e.g., research to develop or test interventions or diagnostic tests, based on new findings from basic aging research or other basic research; studies to improve understanding of mechanisms contributing to clinical or functional findings).
- Promote translation of clinical research findings into practice in relevant health care settings.
- Collaborate substantially with other OAICs on multicenter projects, such as integrating data systems, supporting multicenter observational studies, and providing infrastructure to support multisite clinical trials, including pragmatic trials.
- Where possible, interface with the NIA Research Centers Collaborative Network (RCCN)[2336] and other NIA-funded programs and centers (e.g., Resource Centers for Minority Aging Research,[2337] Centers on the Demography and Economics of Aging,[2338] Roybal Centers,[2339] ADRCs,[2340] and Nathan Shock Centers[2341]).
- Leverage institutional resources, including other NIH-supported programs and centers, to achieve the OAICs' aims efficiently.
- Serve as a source of advice and collaboration to other investigators, both locally and on a large scale, regarding technology, methodology, analysis, or other expertise.

NIH Funding for FY 2016, FY 2017 and FY 2018

NIH funding for the OAICs was $14.25 million in FY 2016, $13.74 million in FY 2017, and $14.59 million in FY 2018.

FY 2016, FY 2017, and FY 2018 Progress Report

Programmatic Activities and Outcomes

- The University of Florida OAIC focuses on optimization of physical performance and mobility in older persons, with the ultimate goal of maintaining independence among this population. University of Florida researchers examine these issues from interdisciplinary perspectives across

[2336] https://www.rccn-aging.org/.
[2337] http://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar.
[2338] http://www.nia.nih.gov/research/dbsr/centers-demography-and-economics-aging.
[2339] http://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging.
[2340] http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers.
[2341] http://www.nia.nih.gov/research/dab/nathan-shock-centers-excellence.

the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral and social sciences, and epidemiology.

- The Boston OAIC fosters collaborations among multidisciplinary teams of investigators from Harvard Medical School, Boston University, and Tufts University to foster function-promoting therapies, or pharmacologic, physical, nutritional, technological, and behavioral interventions that reduce the burden of disabling functional limitations in older adults.
- The University of Pittsburgh OAIC provides support and resources for investigators to identify interventions to optimize mobility and balance and prevent fall-related injuries in the elderly. This OAIC provides an integrated, multidisciplinary approach by pooling resources from five schools at the University of Pittsburgh. The OAIC is currently conducting several studies of interventions to improve balance and mobility, prevent falls, and prevent fall-related injuries.
- The theme of the Duke University OAIC is to understand and understand and optimize reserve and resilience among older adults. Investigators at the Duke OAIC conduct translational studies to understand and enhance people's ability to withstand or recover from functional decline following acute or chronic health stressors.
- The Johns Hopkins University OAIC supports research to determine the causes of and potential interventions to reduce frailty in older adults. A major recent focus of research has been the characterization of potential causes of frailty, as well as pharmacological and behavioral interventions.
- The theme of the UCLA OAIC is "Inflammation, Aging, and Independence." The center aims to determine how inflammatory markers change with normal aging and disease and how these changes affect diseases and outcomes related to independence; link inflammatory markers to genetic and epigenetic profiles; and develop and test interventions to decrease inflammation and improve health and function.
- The University of Maryland, Baltimore OAIC is studying rehabilitation approaches involving exercise and motor learning. The goal is to improve the recovery of older adults who have suffered a stroke, hip fracture, or other chronic debilitating condition. The OAIC plans to translate these findings into effective community-based rehabilitation programs.
- Research at the University of Texas Medical Branch OAIC focuses on identifying predictors of physical function and recovery from illness in older adults, identifying novel treatments to improve function and accelerate recovery, and using clinical trials to assess the efficacy of these treatments in older patients.
- The Wake Forest University OAIC's mission is to assess the risk factors for physical disability in older adults and to develop and test effective preventive interventions, with an emphasis on risk factors and preventive interventions focusing on skeletal muscle. Wake Forest also hosts the Coordinating Center for the National Pepper Center Program.
- The Yale University OAIC's research focuses on investigating geriatric health conditions that have several causes. This focus includes single conditions resulting from several contributing factors or affecting several outcomes, as well as multiple conditions occurring at the same time.
- The University of Michigan OAIC, the first OAIC funded by NIH, advances research on older adults' health care problems. Its current research emphases include understanding how metabolic

factors and inflammation interact with age-related diseases and comorbidities to determine key health outcomes related to mobility and functional status, as well as translational research on the interaction of metabolic factors and inflammation with age-related diseases and comorbidities to improve health outcomes related to mobility and functional status.

- The Mount Sinai School of Medicine OAIC focuses on pain management and palliative care. Investigators with this center conduct pilot and exploratory studies aimed at understanding and ameliorating pain in older adults. The Mount Sinai OAIC is also developing the infrastructure for population-based research on pain and palliative care.
- The University of California, San Francisco (UCSF) OAIC focuses on disability in older people. Its investigators are exploring what leads to disability, how to prevent disability, and how to ameliorate disability's impact on patients and caregivers. This OAIC is particularly interested in the needs of the most vulnerable elders, whether they are vulnerable because of complex medical circumstances or because of adverse social circumstances.
- Translation of basic research findings into clinical interventions that will benefit older Americans is the focus of the new OAIC at the University of Texas Health Science Center at San Antonio (UT Health San Antonio). Current pilot projects include both preclinical and clinical studies.

Research Activities and Outcomes

- Investigators at the UT Health San Antonio OAIC, in collaboration with the Mayo Clinic and the Wake Forest OAIC, were the first to demonstrate that drugs known as senolytics, which remove damaged and non-dividing cells that often accumulate in aging tissues, may be effective in treating idiopathic pulmonary fibrosis (IPF). IPF is a progressive and irreversible disease that results in scarring of the lungs; median survival in patients is less than 5 years after diagnosis. In this pilot study, 14 participants received two senolytic drugs, dasatinib and quercetin, for 3 weeks. At the end of that time, investigators observed modest but significant improvements in the participants' mobility as measured by the distance participants could walk in 6 minutes. Although the study population was very small and the study was not placebo controlled, these encouraging results set the stage for larger randomized, controlled trials in the future.[2342]
- Age is the strongest risk factor for both physical disability and AD/ADRD. Furthermore, evidence is accumulating that common pathways are involved with both physical disability and cognitive impairment. In December 2016, representatives from the OAICs and the NIA-supported ADRC held a joint workshop to explore potential areas of synergy between the two programs' research interests. Participants identified a number of key knowledge gaps and research priorities, including the incorporation of both physical and cognitive functional assessments in clinical care; the contribution of comorbid health conditions to cognitive and physical decline; and the lack of data on the aging process in minority and/or low socioeconomic populations. [2343]
- Advance care planning (ACP) helps ensure that medical care is aligned with the patient's values and has been shown to increase patients' satisfaction with their care. However, most older adults,

[2342] Justice JN, et al. *EBioMedicine* 2019;40:554-63, 2019. PMID: 30616998.
[2343] Brinkley TE, et al. *J Gerontol A Biol Sci Med Sci* 2018;73:1229-37. PMID: 29982466.

including those with serious illness, do not engage in ACP. The issue is particularly acute among minorities, patients with limited English proficiency, and patients with limited health literacy. The UCSF OAIC has pioneered an easy-to-read advance directive and a patient-directed, interactive, online ACP program in English and Spanish called PREPARE For Your Care (PREPARE).[2344] PREPARE is designed to be used at home to prepare people for complex medical decision-making, and it incorporates several unique health communication elements. A recent evaluation demonstrated that the patients randomized to visit PREPARE (vs. receiving an easy-to-read advance directive alone) were more likely to document ACP and were more likely to remain engaged in the ACP process. These results held true among both English and Spanish speakers and among individuals with limited health literacy.[2345]

- Each year, one out of three adults age 65 and older falls, and a third of those falls result in moderate to severe injury. A number of the OAICs, in partnership with the PCORI, have established the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) trial, a randomized pragmatic trial of an individually tailored falls prevention program among community-dwelling older adults. Recruitment for this study was completed in 2017, and the study is ongoing.[2346]

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the OAICs

In 2015, NACA reviewed the NIA Division of Geriatrics and Clinical Gerontology, where the OAICs are administratively housed, and made several relevant recommendations, including the following:

- Facilitate translational efforts by creating a mechanism to bring together directors of all NIA-sponsored centers (e.g., Pepper, Shock, Roybal, Alzheimer's, Minority Aging, Demography) and possibly some non-NIA centers, around critical themes that cross divisions; sponsor post-meeting funding initiatives that mandate investigators from different fields.
- Leverage partnerships by supporting interactions of the Pepper Centers with other NIA-sponsored centers.

In 2018, NIA established RCCN. Led by the American Federation for Aging Research and investigators at Wake Forest School of Medicine, RCCN is a new resource that aims to bridge the NIA's six centers' programs[2347] and promote collaborations across center areas. In its first year, the RCCN initiated a webinar series targeting early-career faculty affiliated with the centers' programs in order to build awareness of available collaborative resources. The Network also established a series of cross-disciplinary conferences

[2344] https://prepareforyourcare.org/.
[2345] Sudore RL, et al. *JAMA Intern Med* 2018;178:1616-25. PMID: 30383086.
[2346] http://www.stride-study.org/.
[2347] In addition to the OAICs, NIA supports the Alzheimer's Disease Research Centers; the Nathan Shock Centers of Excellence in the Basic Biology of Aging; the Resource Centers for Minority Aging Research; the Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences of Aging; and the Centers on the Demography and Economics of Aging.

that will be relevant to at least four centers' programs. The first of these, on achieving and sustaining behavior change, was held in December 2018.

Evaluation Plans

NIH program staff review the progress of each OAIC every year as part of the noncompeting renewal process. In addition, each year, each OAIC must convene an external advisory board of expert scientists from outside the OAIC institution(s) to evaluate progress and suggest any necessary changes in its scientific or administrative directions to achieve its stated goals.

Future Directions

NIH plans to continue to fund new and existing Claude D. Pepper OAICs and to continue to develop and strengthen key areas of aging research in order to discover new and effective ways to promote healthy and productive aging.

Table 2. Current Claude D. Pepper Older Americans Independence Centers

Institution and Location	Year Established
University of Michigan, Ann Arbor, MI	1989
University of California, Los Angeles, CA	1991
Wake Forest University, Winston-Salem, NC	1991
Duke University, Durham, NC	1992[2348]
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994
The University of Texas Medical Branch, Galveston, TX	1999
Johns Hopkins University, Baltimore, MD	2003
University of Pittsburgh, Pittsburgh, PA	2004
University of Florida, Gainesville, FL	2007
Boston University, Boston, MA	2008
Mt. Sinai Medical Center, New York, NY	2010
University of California, San Francisco, CA	2013
The University of Texas Health Science Center, San Antonio, TX	2015

[2348] A Center for the Study of Aging was started at Duke University in 1955; it was designated a Claude D. Pepper OAIC in 1992.

Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

Establishment of the Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

The *Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act*, P.L. 107-84) included provisions for expanding and intensifying research on the muscular dystrophies and mandated that NIH establish Centers of Excellence for muscular dystrophy research. In the *Omnibus Appropriations for FY 2004* (P.L. 108-199), Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs), in honor of the former Minnesota senator who was a driving force behind the MD-CARE Act. The *MD-CARE Act of 2008* officially renamed the centers.

How the Wellstone MDCRCs Function Within the NIH Framework

Centers active in FY 2016–2018 are listed in Table 3. NIAMS, NICHD, and NINDS historically have funded the Wellstone MDCRCs through the U54 Specialized Centers Cooperative Agreement award mechanism; they began using the P50 grant mechanism for awards made in FY 2018 to better align the MDCRCs with NIH policy and similar centers across NIH. NHLBI has also co-sponsored competitions for Wellstone MDCRCs since 2007. It co-funds two centers and plans to support future MDCRC projects, contingent on the availability of funds and meritorious applications that align with NHLBI's mission.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles. Many dystrophies also affect other organ systems, such as the heart, brain, blood vessels, and gastrointestinal tract (stomach and intestines). Some forms occur in infancy or childhood, while others typically appear in middle age or later. The Wellstone MDCRCs address a variety of muscular dystrophies, including the following:

- *Duchenne and Becker muscular dystrophies (DMD).* DMD is the most common childhood form of muscular dystrophy and is an X-chromosome-linked disease. The disease primarily affects males, because they carry only one X-chromosome, meaning that there is no chance for expression of a normal copy of the dystrophin gene (females have two X-chromosomes, one of which may be normal). Boys who have DMD do not produce dystrophin, which muscle cells need to function properly. DMD usually becomes evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their 20s. Becker muscular dystrophy, a less severe disease, occurs when the body produces low levels of dystrophin or forms of dystrophin that do not work properly.

- *Myotonic dystrophy.* Myotonic dystrophy is commonly an adult form of muscular dystrophy, although forms of this disease can affect newborns and other children. It is marked by myotonia (an inability to relax muscles after they contract) and muscle wasting and weakness. Myotonic dystrophy's severity and symptoms vary. It can affect skeletal muscles and other body systems, including the heart, endocrine organs (organs that release hormones into the bloodstream), eyes, brain, and gastrointestinal tract.
- *Facioscapulohumeral muscular dystrophy (FSHD).* FSHD initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral). Symptoms usually develop in the teenage years. Some affected individuals become severely disabled. Wasting of muscles of the trunk can lead to life-threatening breathing complications.
- *Congenital muscular dystrophies (CMDs).* The CMDs are a group of muscular dystrophies with different genetic causes. Muscle weakness is present at birth. Several forms are caused by defects in the interactions of muscle cells with the surrounding extracellular matrix. The brain and other organs are often affected.
- *Limb-girdle muscular dystrophies (LGMDs).* All LGMDs show a similar distribution of muscle weakness, affecting both upper arms and thighs. Scientists have identified many forms of LGMDs caused by mutations in many different genes; some affect children, and others affect adults. A genetic diagnosis is determined for only about half of LGMD patients, suggesting that other genes associated with this condition have not yet been identified.
- *Miyoshi myopathy.* Miyoshi myopathy causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of LGMD, suggesting that research progress in one form of muscular dystrophy could lead to a better understanding of other forms as well.

Such treatments as physical therapy, use of devices for support, corrective orthopedic surgery, and drugs can reduce symptoms and improve quality of life for some people who have muscular dystrophy. Some drugs, such as corticosteroids, can slow the progression of DMD to some extent but have adverse side effects. In September 2016, the FDA approved eteplirsen to treat boys whose DMD is caused by specific gene variants. A variety of other treatment strategies for muscular dystrophies—including gene and cell therapies, drugs, and biologics—are being developed and tested in animal and cell models. Clinical trials for some candidate therapeutics are underway; a few trials have been completed. Due to the level of activity in the muscular dystrophy research field, clinical trial results and new drug applications are likely to continue to increase.

Burden of Illness

An estimated 1 of every 5,600 to 7,700 males in the U.S. ages 5 through 24 has DMD.[2349] Myotonic dystrophy affects approximately 1 in 8,000 people worldwide.[2350] FSHD affects approximately 1 in 20,000 people and affects men and women equally.[2351]

The *MD-CARE Act* called for CDC to collect and analyze information on the muscular dystrophies' incidence and impact. The *Paul D. Wellstone MD-CARE Act Amendments of 2014* (P.L. 113-166) expressed continued support for this effort.

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs promote communication and collaboration, develop and share research resources, and help train new muscular dystrophy researchers. Each center can conduct a mixture of basic research to understand the diseases, translational research to turn basic research findings into interventions for patients, and clinical studies to determine how the diseases affect patients and to test interventions. The overall focus of the Wellstone MDCRCs is to integrate activities to develop therapies and other strategies to reduce the impact of muscular dystrophies on patients and their families.

Collectively, the Wellstone MDCRCs conduct research on various forms of muscular dystrophy, including some not listed above. Examples of research topics addressed by the Wellstone MDCRCs in FY 2016, FY 2017, and FY 2018 follow:

- At the University of Rochester MDCRC, which successfully recompeted for funding in FY 2018, researchers are examining cellular and molecular factors that contribute to myotonic dystrophy's effects on multiple organ systems, including the heart, and are identifying clinical endpoints and biomarkers for use in clinical trials.
- Research at the University of Iowa MDCRC focuses on understanding the causes of and developing treatments for a group of dystrophies called dystroglycanopathies, which are associated with defects in muscle proteins known as dystroglycans. These diseases include some LGMDs, CMDs, and Miyoshi myopathy.
- Projects at the University of Florida MDCRC, which also includes investigators from Northwestern University and UCLA, focus on the roles of inflammation, fibrosis, and fat infiltration in muscular dystrophy and on identifying strategies to counter these processes.
- The Wellstone MDCRC at the University of Massachusetts continues to partner with investigators at Children's Hospital in Boston, the Kennedy Krieger Institute, and Children's Institute at Nationwide Children's Hospital on studies of molecular, genetic, and epigenetic pathologies of

[2349] https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy.
[2350] http://ghr.nlm.nih.gov/condition/myotonic-dystrophy.
[2351] https://ghr.nlm.nih.gov/condition/facioscapulohumeral-muscular-dystrophy.

FSHD, with the goal of developing potential therapies that can be tested clinically. This center also successfully competed for funding in FY 2018.

- The center funded through the University of Washington and Fred Hutchinson Cancer Research Center supports a research team that includes scientists from Seattle Children's Hospital and the University of Rochester. This center also successfully competed for funding in FY 2018. It focuses primarily on preclinical and clinical studies of DMD and FSHD and provides viral and plasmid vectors for studies in small and large animal models to investigators across the country.
- Investigators at the University of Texas Southwestern Medical Center (UT Southwestern), the newest Wellstone MDCRC, are exploring whether a technique that combines the CRISPR/Cas9 system of genomic editing with the ability to generate iPSCs could be used to treat DMD, including DMD-associated cardiomyopathy.

Each Wellstone MDCRC has core facilities that provide unique resources or services for the muscular dystrophy research community. Cores include repositories of research data and biologic samples from patients with different types of muscular dystrophy, assistance with gene therapy development and production, and tools for measuring muscle health and strength in mouse models.

NIH Funding for FY 2016, FY 2017, and FY 2018

NIH funding for the Wellstone MDCRC program was $8.9 million in FY 2016, $8.8 million in FY 2017, and $9.2 million in FY 2018.

FY 2016, FY 2017, and FY 2018 Progress Report

Programmatic Activities and Outcomes

Three Wellstone MDCRCs successfully competed for an additional 5 years of support in FY 2018: the University of Rochester; the University of Massachusetts/Children's Hospital, Boston; and the University of Washington/Fred Hutchinson Cancer Research Center.

The Wellstone MDCRC program has provided opportunities for public–private partnerships in muscular dystrophy. Productive collaborations between the centers and patient advocacy groups (PAGs) continue to promote patient participation and a patient voice in the conduct of research. For example, the Iowa MDCRC hosts an annual patient and family conference, during which researchers provide updates on scientific advances and patients provide data and biospecimens. The Rochester MDCRC hosts local myotonic dystrophy and FSHD patient meetings and sends a biannual newsletter to registry participants. Several centers have industry collaborators. For example, the UT Southwestern MDCRC established the company Exonics Therapeutics to develop CRISPR-based therapeutics for DMD, and this company was recently acquired by Vertex Pharmaceuticals to continue to advance this treatment strategy.

All centers supported in FY 2016, FY 2017, and FY 2018 have formal training and education cores. These facilities provide stipends to predoctoral and postdoctoral researchers and enhance the institutions'

environments for training students, fellows, and early-stage investigators in muscular dystrophy research. This requirement for stipend support is being phased out in FY 2020 to better allow centers to provide additional training opportunities that can be leveraged by the entire muscular dystrophy scientific community.

The Wellstone MDCRC core facilities are national resources for the muscular dystrophy research community. The facilities have been publicized at national meetings and through center websites and the Wellstone MDCRC website.[2352] These shared research tools foster collaborations across departments and schools within institutions, and among investigators and health care providers nationwide. Examples of these facilities include the following:

- The University of Rochester's National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy, which contains information about more than 2,400 patients, provides researchers with cell and tissue samples and clinical information about the donors of these samples. Between 2014 and 2018, the registry facilitated 22 clinical studies by 15 different investigators at 10 research sites.
- The University of Iowa Wellstone MDCRC oversees a Muscle Tissue/Cell Culture/Diagnostics Core that serves as a national tissue and cell culture resource for research, as well as a laboratory for patient diagnostic and post-intervention biopsy evaluation for clinical trials. A repository contains muscle biopsies from approximately 4,000 patients with various neuromuscular disorders. It also contains fibroblast cultures established from approximately 175 muscular dystrophy patients, which investigators will provide to other scientists upon request.
- The Physiological Assessment Core at the University of Florida evaluates muscle integrity and function in mouse models of muscular dystrophy. The facility's staff conduct measurements that are the standard for showing whether a potential treatment is effective in animal models.
- The University of Massachusetts Wellstone MDCRC maintains a repository of tissues collected from FSHD patients and unaffected relatives. It can provide characterized FSHD cells and control muscle cells to laboratories studying FSHD or other muscular dystrophies. In FY 2018, the center began providing animal models of FSHD to the research community as part of its core facility.
- The University of Washington Wellstone MDCRC provides viral and plasmid vectors for studies involving the development and testing of potential therapies in small and large animal models. Services offered include consulting, reagents, and training related to vector production.
- The UT Southwestern Wellstone MDCRC provides a comprehensive electronic database that investigators can use to optimize exon-skipping strategies to rescue dystrophin expression in skeletal and cardiac muscle cells derived from iPSCs.

Research Activities and Outcomes

The Wellstone MDCRCs conduct high-quality translational and clinical studies to advance understanding of and therapy development for a variety of muscular dystrophies. Several active clinical trials in the

[2352] http://www.wellstonemdcenters.nih.gov/index.htm.

muscular dystrophies were made possible by Wellstone MDCRC findings. Discoveries by investigators affiliated with the Wellstone MDCRC programs also form a basis of new conceptual models, with potential impacts on therapy development for the dystrophies, other neuromuscular diseases, and additional conditions.

Examples of accomplishments in FY 2016, FY 2017, and FY 2018 are provided below:

- The University of Rochester MDCRC completed a 3-year natural history study in 80 patients. Data collected through this study facilitated the development and validation of a patient-reported outcome measure called the Myotonic Dystrophy Health Index (MDHI).[2353] Also in preparation for additional clinical trials in myotonic dystrophy, this center completed a study of muscle biopsies from 44 myotonic dystrophy type 1 patients and 11 healthy controls that established a panel of gene expression changes as a quantitative biomarker of molecular pathology of this disease that can be used to assess the effects of candidate therapeutics.[2354]
- The University of Iowa MDCRC has advanced understanding of the molecular mechanisms for how mutations in any of several different genes cause dystroglycanopathies and how these genes are responsible for a specific modification of a muscle membrane receptor that is required for binding to matrix proteins.[2355,2356] This detailed structural understanding may contribute to the development of novel therapeutics for muscular dystrophies and has also advanced understanding of how viruses use these membrane receptors to infect cells. Further clinical studies of congenital muscular dystrophy and other dystroglycanopathies have led to the characterization of additional mutations.[2357] Patient samples collected by the University of Iowa MDCRC have facilitated studies to identify serum biomarkers for dystroglycanopathies.
- Investigators at the University of Florida Wellstone MDCRC published several papers describing factors that influence muscle damage and repair in animal models of muscular dystrophy and potential strategies to prevent damage or stimulate repair.[2358–2360] In one such study, investigators examined how glucocorticoid steroids affect cell membrane repair in mice and demonstrated that a single dose of glucocorticoid steroids improved membrane repair in injured muscle by upregulating two genes involved in cell membrane repair.[2361] The research team found that weekly dosing activated additional muscle-enhancing pathways, while daily dosing conversely activated cellular pathways that cause muscle to shrink and weaken. If glucocorticoid steroids produce a similar response in humans, this study could directly inform the dosing of DMD patients to maximize the drugs' beneficial effects while minimizing their negative side

[2353] Heatwole C, et al. *Muscle Nerve* 2016;53(2):183-90. PMID: 26044513.
[2354] Wagner SD, et al. *PLoS Genet* 2016;12(9):e1006316. PMID: 27681373.
[2355] Briggs DC, et al. *Nat Chem Biol* 2016;12(10)810-4. PMID: 27526028.
[2356] Inamori KI, et al. *Glycobiology* 2016;26(12):1284-96. PMID: 27496765.
[2357] Brun BN, et al. *Neuromuscul Disord* 2018;28(7):592-6. PMID: 29759639.
[2358] Capote J, et al. *J Cell Biol* 2016;213(2):275-88. PMID: 27091452.
[2359] Hammers DW, et al. *JCI Insight* 2016;1(21):e90341. PMID: 28018975.
[2360] Quattrocelli M, et al. *PLoS Genet* 2017;13(10):e1007070. PMID: 29065150.
[2361] Quattrocelli M, et al. *J Clin Invest* 2017;127(6):2418-32. PMID: 28481224.

effects. It also could affect treatment strategies for the estimated 1 percent of the entire U.S. population who are treated chronically with glucocorticoid steroids for other conditions.

- Researchers at the University of Massachusetts Wellstone MDCRC have discovered novel signaling pathways and drug targets that modulate DUX4 toxicity in FSHD. These findings are now being applied to drug discovery efforts. The investigators continue to develop and expand cell and animal models that are shared with the community.
- Wellstone MDCRC investigators at the University of Washington and the Fred Hutchinson Cancer Research Center developed an MRI approach for monitoring the replacement of muscle with fat in the legs of FSHD patients.[2362] This advance opens an avenue for researchers conducting clinical trials in FSHD to focus specifically on those muscles undergoing the dystrophic process so that any beneficial effects of future interventions have the best chance of being identified. Other work from the center focuses on testing gene therapy approaches in mouse models of DMD.[2363] Work from this group has directly contributed to at least one current gene therapy clinical trial in DMD.[2364]
- The UT Southwestern Wellstone MDCRC has identified guide RNAs for potential CRSPR/Cas9 treatment of DMD that optimizes exon-skipping strategies to rescue dystrophin expression in iPSC-derived muscle cells and in animal models of DMD.[2365] The center is sharing these data in a comprehensive electronic database, the Duchenne Skipper Database.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDCRCs

Evaluation Plans

NIH began formally evaluating the Wellstone MDCRC program in FY 2018. Although NIH had refined the Wellstone MDCRC program since the program's inception in FY 2003, a comprehensive review at this time was appropriate because of significant changes in the neuromuscular disease research landscape during the intervening 15 years.

To this end, NIH convened a working group of the NIAMS advisory council that reviewed data collected from various sources, including Wellstone MDCRC progress reports, NIH administrative data, information extracted from publications and Wellstone MDCRC websites, interviews with principal investigators and other stakeholders, and a Request for Information that was advertised to the broad research and patient advocacy communities. The working group's charge was to identify best practices for achieving the Wellstone MDCRCs' goals of—

[2362] Ferguson MR, et al. *Muscle Nerve* 2018;57(6):905-12. PMID: 29236297.
[2363] Kolwicz SC Jr, et al. *Mol Ther* 2016;24(2):240-50. PMID: 26388461.
[2364] https://clinicaltrials.gov/ct2/show/NCT03368742
[2365] Amoasii L, et al. *Sci Trans Med* 2017;9(418): pii: eaan8081. PMID: 29187645.

- Supporting basic, preclinical translational, and clinical research in the muscular dystrophies through synergistic projects
- Developing and broadly distributing resources that accelerate muscular dystrophy research
- Facilitating the training of the next generation of muscular dystrophy researchers and clinical scientists
- Enabling connections with the patient community

The working group included researchers and clinicians working in the neuromuscular disease and related fields, with expertise suitable to critically evaluate the research activities, center structures, and training and community outreach activities at the Wellstone MDCRCs. Several members had served as scientific advisors to PAGs and were able to use that perspective to inform working group discussions. The working group's findings were presented at the February 2019 NIAMS Advisory Council meeting.[2366]

Future Directions

NIH is committed to supporting up to six outstanding Wellstone MDCRCs. Based on its funding commitment to the existing centers, NIH has announced an open competition and its intent to fund up to three centers (for a total of up to six active centers) in FY 2020, pending the availability of funds and a sufficient number of highly meritorious applications.[2367]

Recommendations described in the evaluation working group's report were incorporated into the FY 2020 funding opportunity announcement and will be reflected in the Notice of Awards by explicitly stating information that must be included in annual progress reports. For example, the FOA was edited to clarify that research on any muscular dystrophy, not just those listed in previous funding opportunity announcements or in the *MD-Care Act*, is eligible for consideration under the Wellstone MDCRC program. Text encouraging clinical trial readiness, biomarker and clinical outcome assessment measure development and validation, and natural history studies was featured more prominently than in previous announcements.

As noted above, centers that successfully compete for FY 2020 funding will no longer be required to provide stipends to predoctoral and postdoctoral fellows. Instead, they are expected to promote trainee support through individual fellowships or career development awards from public and private funding organizations, organize research meetings for trainees across the network of Wellstone MDCRCs, and organize training activities, such as courses or webinars for the overall muscular dystrophy research community. The centers also are encouraged to provide opportunities for non-clinical students and postdoctoral researchers to be exposed to clinical research. Centers' clinical research projects should involve medical students, clinical fellows, and residents.

Previous funding opportunity announcements have required that the Administrative Core develop a website to publicize the availability of the center's shared resource(s). Additional language was added to

[2366] https://wellstonemdcenters.nih.gov/sites/wellstone/files/WellstoneCenterEvalRptExecSumm-508.pdf.
[2367] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-19-031.html

the latest FOA so that Data and Resource Sharing Plans are better defined regarding the processes for requesting and approving requests and the time between request and delivery. The FY 2020 Notice of Awards will include additional reporting requirements for each request of shared resources.

Table 3. Active Senator Paul D. Wellstone MDCRCs, FY 2016–2018

Institution and Location	Years Funded
University of Rochester, Rochester, NY	2003–present
University of Iowa, Iowa City, IA	2005–present
University of Florida, Gainesville, FL	2005–present
University of Massachusetts, Worcester, and Children's Hospital, Boston, MA	2013–present
University of Washington and the Fred Hutchinson Cancer Research Center, Seattle, WA	2014–present
University of Texas Southwestern Medical Center, Dallas, TX	2015–present

National Institute on Minority Health and Health Disparities Centers of Excellence

Establishment of NIMHD Disparities Centers of Excellence

The Centers of Excellence (COEs) program supported by NIMHD is one of several programs that are central to NIH's scientific investment strategy to improve minority health and ultimately eliminate health disparities. The *Minority Health and Health Disparities Research and Education Act of 2000* (P.L. 106-525) included provisions for the creation of NIMHD to conduct and support research, training, and dissemination of information with respect to racial and ethnic minorities and other populations with health disparities.[2368] The statute specifically mandated the creation of COEs in research institutions to conduct biomedical, behavioral, minority health, and health disparities research and training.

Distinguishing minority health and health disparities provides a platform for research to advance and generate knowledge that can improve the health of minorities and to reduce health disparity conditions across populations. This new strategy to classify each distinctively shows promise for guiding the field into the next generation of minority health and health disparities research.

Minority health is defined as distinctive health characteristics and attributes of a racial or ethnic minority group who is socially disadvantaged or subject to potential discriminatory acts. Minority health

[2368] P.L. 106-525 designated the National Center on Minority Health and Health Disparities (NCMHD). In FY 2010, NCMHD was re-designated as NIMHD by the *Patient Protection and Affordable Care Act* (P.L. 111-48).

populations are classified by the Office of Management and Budget Directive 15 into the following racial and ethnic categories: AI/AN, Asian, Black or African American, Hispanic or Latino, and Native Hawaiian or Other Pacific Islander. Minority health research is the multidisciplinary scientific investigation of distinctive health characteristics and attributes of minority racial or ethnic groups who are usually underrepresented in biomedical research to understand population health outcomes.

NIH defines a health disparity as a health difference that adversely affects disadvantaged populations. Relevant health differences may manifest in the near term and in the longer term. Health disparity long-term outcomes include higher incidence or prevalence of disease, as well as earlier onset or more aggressive progression; premature or excessive mortality from specific conditions; greater global burden of disease as indicated by population health measures; poorer health behaviors and clinical outcomes associated with disease; and worse self-reported outcome measures that reflect daily functioning, quality of life, or symptoms from specific conditions.

The difficulty of achieving these outcomes suggests the need for a focus on long-term outcomes in the following areas:

- Risk to well-being (e.g., unhealthy behaviors, such as smoking; stress; obesity; racism or discrimination; unhealthy environmental conditions; less education; disadvantaged SES; limited language proficiency; poor nutrition; greater number of incidents that affect health, including violence, accidents, and injury)
- Biological/epigenetic risk (e.g., earlier age of disease onset, presence of predisposing gene variants, metabolic differences, susceptibility, faster disease progression, greater disease severity)
- Clinical event risks that adversely impact health, including quality indicators of health services (e.g., differential treatment results, poor physician-patient communication, different treatment offered, poor management of comorbidities, poor symptom management, adverse events caused by medications)
- Utilization-of-care risks (e.g., lack of access to services; later stage of diagnosis, use/abuse of appropriate services; underutilization of health care services; lack of screening; greater number of hospitalizations and readmissions; need for primary/specialty care; lack of primary care home, emergency room visits, end of life/palliative care)

Health disparity populations include racial and ethnic minorities, people with low SES, residents of rural areas, sexual and gender minorities, and others subject to discrimination who have poorer health outcomes often attributed to being socially disadvantaged, resulting in these groups' being underserved in the full spectrum of health care. Health disparities research is a multidisciplinary field of study devoted to gaining greater scientific knowledge about the influence of health determinants, understanding the role of different pathways leading to disparities, and determining how findings translate into interventions to reduce health disparities.

NIMHD COEs address health disparities through the following strategies:

- Conducting and supporting clinical, health services, population health, and behavioral research
- Promoting enhancement of research infrastructure and research training
- Providing community engagement and dissemination of research information to racial and ethnic minority and other communities that experience health disparities

How the NIMHD COEs Function Within the NIH Framework

NIMHD established the COEs to create a comprehensive platform in academic institutions to address health disparities in priority diseases and conditions by conducting research, training a diverse scientific workforce, and engaging the community. The COEs support the *HHS Action Plan to Reduce Racial and Ethnic Health Disparities*[2369] and the *National Prevention Strategy*.

Since 2002, NIMHD has supported 103 COEs in 35 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands (Table 4 provides the locations of current COEs). Initially, the program used three different funding mechanisms: Resource-Related Centers (R24), Exploratory Centers (P20), and Comprehensive Centers (P60). Using these different funding mechanisms allowed NIMHD to support institutions with varying levels of biomedical research expertise and capacity. This approach also enabled NIMHD to support geographically and culturally diverse institutions that have long-standing partnerships with local and regional communities and organizations addressing health disparities.

In FY 2017, NIMHD released a new FOA for the COE program titled *NIMHD Specialized Centers of Excellence on Minority Health and Health Disparities*,[2370] using the U54 mechanism. This initiative aims to advance the science of minority health and health disparities by conducting transdisciplinary, multilevel research in a defined thematic area and providing research opportunities and support for postdoctoral fellows, junior faculty, and other investigators.

NIMHD supported 40 COEs in FY 2016, 16 COEs in FY 2017, and 14 COEs in FY 2018. All COEs funded since 2005 have had project periods of 5 years. The types of institutions funded directly by the NIMHD COE program or through partnerships with NIMHD COEs include research-intensive institutions, medical schools, historically Black colleges and universities, and Hispanic-serving institutions. NIMHD COEs have also been successful in developing novel partnerships with different types of nonacademic institutions, such as community-based organizations, local departments of public health, and local school districts. These partnerships provide a means for nonacademic institutions to engage in research on improving minority health and eliminating health disparities.

Description of Disease or Condition

The research and other COE activities that NIMHD supports are not limited to or focused on a single disease, illness, or condition. The COE program supports collaborative minority health and health disparities research to identify biological, behavioral, sociocultural, environmental, and health system

[2369] http://www.minorityhealth.hhs.gov/npa/files/Plans/HHS/HHS_Plan_complete.pdf.
[2370] https://grants.nih.gov/grants/guide/rfa-files/rfa-md-17-005.html.

factors that contribute to disparities, and to develop evidence-based interventions to reduce targeted health conditions—such as CVD, hypertension, stroke, cancer, diabetes, HIV/AIDS, severe mental disorders, youth suicide, substance use, and obesity—that disproportionately affect racial and ethnic minority and other health disparity populations. NIMHD solicitations for COEs encompass not only diseases or conditions that disproportionately affect health disparity populations but also factors that influence health. The thematic research foci of the currently funded COEs include sociocultural factors that affect health disparity populations, such as trauma and violence, intergenerational transmission of racialized stress, health literacy, the role of social networks, access to health care, and resilience through the life course.

Burden of Illness

The diversity of the contemporary American population is one of the nation's greatest assets. However, the richness of this diversity is challenged by the disproportionate burden of disease and illness that health disparity populations experience. Compelling evidence of the disparities affecting the U.S.'s racial and ethnic minority, economically disadvantaged, and rural populations includes lower life expectancies and higher rates of cancer, birth defects, developmental disorders, infant mortality, asthma, diabetes, obesity, CVD, and stroke. Populations that suffer from health disparities also bear a disproportionate burden of morbidity and mortality associated with HIV/AIDS, autoimmune diseases (such as lupus and scleroderma), poor oral health, sexually transmitted diseases, mental disorders, violence, and substance use.

Scope of NIH Activities: Research and Programmatic

Guided by the NIMHD Minority Health and Health Disparities Research Framework (Research Framework),[2371] the scope of activities conducted by NIMHD COEs is based on a thematic focus that identifies key factors relevant to understanding and promoting minority health and the elimination of health disparities. Successful COE applications reflect the NIMHD Research Framework by addressing the intersection of domains of influence (biological, behavioral, physical environment, sociocultural environment, and health care system) and levels of influence (individual, interpersonal, community, and societal). This broad scope provides considerable flexibility for COEs to design and implement the multi- and transdisciplinary strategies, studies, interventions, and activities needed to reduce and, ultimately, eliminate health disparities. The NIMHD COE program requires all COEs to establish certain cores:

- An Administrative core for carrying out and overseeing administrative matters and functions
- An Investigator Development core that requires pilot awards and research support for early-stage investigators, junior faculty, and postdoctoral fellows
- A Research Projects core for conducting, coordinating, generating, and advancing research on minority health and health disparities with one to three observational or interventions studies

[2371] https://nimhd.nih.gov/about/overview/research-framework/.

- A Community Engagement and Dissemination core to facilitate equitable collaborative and sustainable relationships with the community and other stakeholders in research and dissemination of effective health information messages and research findings

NIH Funding for FY 2016, FY 2017 and FY 2018

NIH funding for the NIMHD COE program was $46.2 million in FY 2016, $20.9 million in FY 2017, and $17.9 million in FY 2018. During FY 2016 to FY 2017, NIMHD COEs transitioned to a new funding mechanism, the cooperative agreement U54.

FY 2016, FY 2017, and FY 2018 Progress Report

Programmatic Activities and Outcomes

Significant programmatic accomplishments include the establishment of 12 new COEs. Forty NIMHD COEs were active in FY 2016, 16 in FY 2017, and 14 in FY 2018 (Table 4).

Research Activities and Outcomes

Funding for the NIMHD COEs has produced several research accomplishments for FY 2016, FY 2017, and FY 2018.

The Case Western Reserve University's COE focused on involving communities and institutions in delivering and disseminating evidence-based health disparity interventions related to kidney transplantation and organ donation. One research project studied the mechanisms through which CHWs can improve hypertension management for African American patients, while another project examined whether using community members as manuscript reviewers can increase the community relevance of health disparities–related journal articles. In another study, investigators examined organ donation consent by directly verifying donor designation on driver's licenses and comorbid conditions recorded in electronic health records. Driver's license donor designation (46 percent) was lower than in studies of self-reported willingness (66 percent). Individuals who were women, non-Hispanic White, English or Spanish-speaking, employed, and privately insured were more likely to be designated as donors. Findings suggest more research and efforts on organ donation should be tailored to specific subgroups.[2372]

The Clark Atlanta University's COE is committed to understanding the underlying causes of prostate cancer disparities among African American men. African American men have 1.6 times higher incidence and 2.5 times higher mortality rate for prostate cancer than White men. Recent studies show that the determinants of this high incidence and aggressiveness of prostate cancer seen in African Americans are associated with genetic and molecular level differences that result in racial disparities in prostate cancer incidence and outcomes seen in African American men. One study measured the levels of transforming

[2372] Sehgal NK, et al. *Am J Transplant* 2016;16(4):1294-7. PMID: 26603147.

growth factor β (TGFβ) and included 200 patients with prostate disease, 150 African American and 50 White men. TGFβ functions as a tumor suppressor in normal epithelial cells and early-stage cancer by inhibiting proliferation of cancer cells. However, in later stages of the prostate disease, the growth inhibitory function of TGFβ is lost, and TGFβ functions as a tumor promoter and is associated with aggressive forms of cancers. African American and prostate cancer patients had higher levels of TGFβ3 protein than African American healthy controls and White patients. Studies on prostate cancer cell lines from African Americans revealed that TGFβ3 protein levels were also higher in these cells compared to prostate cancer cell lines from Whites. The study also found that TGFβ did not inhibit cell proliferation or tumor growth as it is supposed to function in African American-derived cells. It induced cell migration and metastasis in African American–derived prostate cancer cells. The study indicates that development of aggressive prostate cancer in African American men could be due to an increased level of this protein that loses the tumor suppressive properties. This study was a collaboration between researchers at Clark Atlanta University and Fox Chase Cancer Center. This COE has also worked closely with the local community to share research findings on prostate cancer.[2373]

The New York University School of Medicine's COE seeks to understand, address, and reduce health disparities among Asian Americans. Few interventions for diabetes behavioral management have been culturally and linguistically adapted for South Asians. Interventions using CHWs have been effective in controlling diabetes in African American and Hispanic or Latino populations but have not been tested in Asian populations. One study will evaluate the effectiveness of a multilevel intervention involving CHWs, compared to usual care in improving diabetes management among South Asian patients with uncontrolled diabetes. Investigators will work with 25 primary care practice settings to recruit participants. This project will build on prior research from the COE that has demonstrated acceptability and efficacy of a CHW-led diabetes management intervention in community settings to improve health behaviors among South Asians. This multilevel intervention will leverage health information technology tools to support integration of CHWs with health care teams; encourage feedback between health care providers and CHWs; and establish a referral mechanism between CHWs, patients, and community resources. The study will use an electronic health records–based registry system to identify patients with uncontrolled diabetes and individual and family-based approaches to improve diabetes self-management among patients.[2374]

The University of Pennsylvania's COE studied disparities in prostate cancer outcomes and developed interventions to address these disparities between African American and White men. The COE conducted research to identify biological, behavioral, social, environmental, geospatial, and health care factors that influence prostate cancer outcomes. One study measured access to care across multiple dimensions to determine whether access contributed to racial differences in prostate cancer among 2,374 men with localized prostate cancer. Findings showed 85 percent of men received definitive treatment with no differences by race, while African American men were less likely to report receiving high-quality care or have good doctor–patient communication compared with White men. Overall, access did not explain

[2373] Elliott B, et al. *Carcinogenesis* 2018;39(4):546-55. PMID: 29474521.
[2374] https://projectreporter.nih.gov/project_info_description.cfm?aid=9484499&icde=0.

racial differences, although access was related to perceived quality of care and better doctor–patient communication. [2375]

The University of Washington's COE is committed to addressing the health of AI/AN individuals, including health disparities, and to developing a cohort of AI/AN behavioral scientists. The Tribal College and University (TCU) Student Epidemiology Study focused on the prevalence of suicide risk among TCU students and will use findings to develop or adapt suicide prevention approaches that can be targeted to individuals at high risk for suicide. This study was undertaken in collaboration with the American Indian Higher Education Consortium, 22 TCUs, and 3 research centers at the University of Washington. The Healthy Hearts 2 randomized controlled trial evaluated a culturally adapted, motivational interview–based, cognitive-behavioral intervention to reduce depression and CVD risk among AI/AN individuals with prediabetes or diabetes. The *Vr2L 2Spirit* study is a novel, theoretically grounded intervention using gamification theory and the internet to provide a rich and complex web-based 3-week HIV and substance misuse prevention intervention among AI/AN MSM. In a private, dedicated virtual space, the participants were exposed to a distributed asynchronous learning environment with contextual AI/AN references to gain HIV and substance use prevention motivation (via private sessions with counselors), information (via learning paths), and skills (via role play challenges). The COE also produced and created curricula and intervention protocols for CVD prevention, treatment of depression, screening and treatment of post-traumatic stress disorder, HIV and sexually transmitted infection risk prevention, alcohol and substance use prevention and treatment, community-based participatory research approaches, and culturally adapted certification to conduct ethical research with AI/AN communities.[2376]

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NIMHD COEs

Since the program's inception in 2002, NIMHD COEs have made progress toward improving minority health and eliminating health disparities. However, much remains to be done in designing and taking the critical steps needed to translate research findings into meaningful actions that will improve the quality of life of people burdened by health disparities. Efforts should be targeted toward interventions that work. NIMHD and its COEs cannot and do not act alone; NIMHD has sought and continues to seek new partners and also has encouraged each COE to establish partnerships with other NIH-funded centers and programs, other federal agencies, and other groups committed to eliminating health disparities. NIMHD will continue to pursue ongoing recommendations, including efforts to achieve the following goals:

- Increase the diversity of the scientific workforce, especially the number of biomedical and behavioral scientists from racial and ethnic minorities and other health disparity populations. Focused efforts are particularly important for increasing the number of scientists and researchers who (1) remain in the sciences beyond the terminal research or professional degree and beyond the postdoctoral or residency stage and who pursue basic or clinical research as a career and (2)

[2375] Pollack CE, et al. *Cancer* 2017;123(22):4449-57. PMID: 28727136.
[2376] https://projectreporter.nih.gov/project_info_description.cfm?aid=9044612&icde=44769670.

serve in leadership and decision-making roles as members of scientific review panels or members of national advisory councils.

- Create opportunities for biomedical and behavioral scientists to work with population scientists, health services researchers, and other public health researchers to more effectively address the transdisciplinary challenges in health disparities elimination and prevention research.
- Enhance the nation's capacity to conduct health disparities research by expanding research and training opportunities.
- Increase outreach, information dissemination, and public education regarding NIH research.

Evaluation Plans

NIMHD program staff evaluate the COEs' annual progress by examining each COE's published peer-reviewed articles and additional NIH research funding obtained by investigators associated with the COE. Additional metrics may include books and book chapters published; conferences sponsored and presentations given on health disparities; community engagement activities, such as health fairs and other forums for disseminating health promotion materials; community participation in research and clinical trials (if applicable); and research training and professional development opportunities provided to emerging scientists. This review determines each COE's progress toward meeting the aims and objectives of its grant and helps identify areas of concern that need to be addressed.

Future Directions

The NIMHD COE program will continue to intensify research efforts to improve minority health and understand, reduce, and eliminate health disparities, with an emphasis on sustaining current partnerships and establishing new ones. With the establishment of new partnerships, NIMHD expects that its COEs will continue to uncover new biomedical and behavioral knowledge for improving minority health and eliminating health disparities across a broad spectrum of diseases and health conditions. It is also expected that NIMHD COEs will embrace future research themes that emphasize the translation of research knowledge into practice and policy.

The COEs will also continue to develop new technologies for measuring the complex interactions between health disparities and social and policy level factors and new paradigms. The resulting knowledge and technologies will lead to the development and implementation of biopsychosocial and other interventions and strategies for improving minority health and eliminating health disparities. Conducting population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the U.S. will continue to be important. NIMHD will continue to support studies to eliminate or decrease the impact of factors that contribute to the excess risks, morbidity, and mortality associated with living in some regions of the U.S.

The success of these and future research efforts by the NIMHD COEs will continue to depend, in part, on the development of improved methodological tools, measures, validated instruments, and novel research designs for teasing out the contribution of biologic, behavioral, and social factors to health disparities, as

well as identifying the role that health policies and practices play in reducing health disparities. The success of these COEs will also depend on collaboration with important stakeholders—including community organizations, local government, and health care systems—to ensure that research findings have true community impact.

Table 4. NIMHD Centers of Excellence Active in FY 2016, 2017, and 2018.

Institution and Location
Arizona State University, Tempe, AZ
Case Western Reserve University, Cleveland, OH
Charles R. Drew University of Medicine and Science, Los Angeles, CA
Clark Atlanta University, Atlanta, GA
Duke University, Durham, NC
Florida Agricultural and Mechanical University, Tallahassee, FL
Florida International University, Miami, FL
The George Washington University, Washington, DC
Georgetown University, Washington, DC
Georgia Southern University, Statesboro, GA
Harvard T.H. Chan School of Public Health, Boston, MA
Howard University, Washington, DC
Jackson State University, Jackson, MS
Johns Hopkins University, Baltimore, MD
Loma Linda University, Loma Linda, CA
Morehouse School of Medicine, Atlanta, GA
New York University School of Medicine, New York, NY
North Carolina Central University, Durham, NC
Northern Arizona University, Flagstaff, AZ
Rush University Medical Center, Chicago, IL

Institution and Location
SUNY Downstate Medical Center, Brooklyn, NY
The University of Alabama, Birmingham, AL
University of Arkansas Medical Sciences, Little Rock, AR
University of California, Los Angeles, CA
University of California, San Francisco, CA
University of Colorado Denver, Aurora, CO
University of Hawaii, Manoa, HI
University of Illinois at Chicago, Chicago, IL
University of Maryland, College Park, MD
University of Massachusetts Medical School at Worcester, Worcester, MA
University of Miami, Coral Gables, FL
University of Michigan, Ann Arbor, MI
University of New Mexico Health Sciences Center, Albuquerque, NM
University of North Texas Health Sciences Center, Fort Worth, TX
University of Oklahoma Health Sciences Center, Oklahoma City, OK
University of Pennsylvania, Philadelphia, PA
University of South Alabama, Mobile, AL
University of the Virgin Islands, St. Thomas, VI
University of Washington, Seattle, WA
Virginia Commonwealth University, Richmond, VA
Wake Forest University of Health Sciences, Winston-Salem, NC
Washington State University, Pullman, WA

Rare Diseases Clinical Research Network

Establishment of the Rare Diseases Clinical Research Network

The *Rare Diseases Act of 2002* (RDA) (P.L. 107-280) directed the Office of Rare Diseases Research (ORDR) at NIH to "enter into cooperative agreements with or make grants for regional centers of excellence on rare diseases." These centers of excellence were initiated in 2003 with the establishment of the Rare Diseases Clinical Research Network (RDCRN) as cooperative agreements for Rare Diseases Clinical Research Consortia (RDCRC) and a Data Management and Coordinating Center (DMCC). These cooperative agreements are 5-year research awards; they are currently completing their third award cycle (RDCRN3), with the fourth cycle of cooperative agreements (RDCRN4) to be awarded in the fourth quarter of FY 2019.

The RDA defines a rare disease as a condition affecting fewer than 200,000 individuals in the U.S. Collectively, an estimated 7,000 diseases or conditions fall into this category; cumulatively, approximately 25 to 30 million people in the U.S. are affected by a rare disease. Most of these disorders are serious or life-threatening and lead to significant morbidity and mortality. Thus, rare diseases are a significant public health concern, and NCATS has been working to help people understand that, given these statistics, rare diseases are really not rare.[2377]

Despite advances in our understanding of the causes and mechanisms of many diseases, effective treatments are available for only a small number of these conditions. FDA-approved treatments exist for approximately 5 percent of these conditions. Although the pace of rare disease therapeutics development has increased in recent years, the approach of addressing and resolving one disease at a time takes too long.

To help address the challenges of developing treatments for rare diseases, RDCRN was established. RDCRN is a collaborative effort that reaches across ten NIH Institutes and Offices: NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NINDS, NIMH, and ODS within the NIH Office of the Director.

The RDCRN program is designed to advance research on rare diseases by promoting highly collaborative, multisite, patient-centric translational and clinical research.

RDCRN supports consortia that conduct—

- Collaborative activities, including multisite longitudinal studies or clinical trials involving individuals with rare diseases
- Training of clinical investigators in rare diseases research
- Pilot and demonstration research projects
- Uniform data collection protocols for rare diseases

[2377] https://ncats.nih.gov/funding/open/rare-diseases-challenge/winners.

- Access to information about rare diseases for basic and clinical researchers, academic and practicing physicians, patients, and the public

DMCC provides infrastructure support for both individual projects and network activities, such as data collections and trial oversight and management.

An important component of RDCRN is the meaningful partnership each consortium is required to maintain with patients or PAGs. The Coalition for Patient Advocacy Groups (CPAG) brings together the stakeholder organizations from all consortia within RDCRN with the intent of leveraging information and resources from across the network.

To date, RDCRN has supported 31 individual consortia that have conducted research on 238 individual disorders, with more than 40,000 research participants, leading to a greater understanding of rare diseases. To learn more about the RDCRN consortia and the DMCC, visit the NCATS website.[2378]

How RDCRN Functions Within the NIH Framework

The current iteration of RDCRN (RDCRN3) includes 21 consortia and the DMCC (Table 5). Each of the 21 consortium centers develops and carries out clinical research on at least three related rare diseases, with oversight from NCATS and participating NIH ICs. A Steering Committee provides guidance to the network and consists of the principal investigator of each consortium and the DMCC, the NCATS RDCRN Program Director, NIH IC program officers, and the chair of the RDCRN CPAG.

Description of Disease or Condition

For the purpose of RDCRN, *rare diseases* may fall into one of the following categories:

- Disorders: physical or mental conditions or ailments
- Syndromes: groups of symptoms that occur together, or a condition characterized by a set of associated symptoms
- Diseases: a disorder of structure or function that affects a specific location and is not a result of physical injury
- Manifestations: symptoms or signs of an ailment
- Conditions: a particular state of being that limits/restricts something else

Approximately 80 percent of rare diseases are believed to be of genetic origin. It is estimated that at least 50 percent of the patients are children.

[2378] https://ncats.nih.gov/rdcrn.

Burden of Illness

The burden of illness for rare diseases is difficult to assess because of the large number of disorders, the complexity of each disease, and the limited availability of prevalence and incidence data. Beyond the individual burden of a specific disorder, families and patients with rare diseases face many of the same challenges, including the following:

- Diagnosis: It can take years or even a decade to receive an accurate diagnosis; this is commonly referred to as the *diagnostic odyssey*.
- Access to experts: Often, few physicians have expertise in any given rare disease, requiring patients to travel great distances for consultations, treatments, or clinical trials.
- Treatment: Often, no treatments are available for the patient. Only a limited number of pharmaceutical and biotech companies conduct research into rare diseases, because it is difficult to recover the costs of developing treatments for small, geographically dispersed populations.
- Social and emotional consequences: Patients and families often feel alone and isolated in navigating the challenges that accompany rare disease diagnosis and treatment.
- Financial burden: Rare diseases represent a disproportionate share of health care spending. The numerous physician visits, tests, expensive treatments (when they do exist), and severity of the illnesses can be financially devastating for families.

Scope of NIH Activities: Research and Programmatic

RDCRN currently supports natural history studies to understand disease origins and progression, clinical trials, and other clinical studies on approximately 200 rare diseases at more than 454 clinical centers across the U.S. and 21 countries, with 144 patient advocacy organizations and 2,600 researchers actively participating.

The RDCRN program currently comprises the following consortia (through approximately July 2019; new and renewed existing consortia under RDCRN4 will be established in August 2019):

- Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium
- Autonomic Disorders Consortium
- Brain Vascular Malformation Consortium
- Brittle Bone Disorders Consortium
- Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)
- Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium (CReATe)
- Developmental Synaptopathies Consortium
- Dystonia Coalition
- Genetic Disorders of Mucociliary Clearance Consortium
- Inherited Neuropathies Consortium
- Lysosomal Disease Network (LDN)
- Nephrotic Syndrome Rare Disease Clinical Research Network

- North American Mitochondrial Disease Consortium
- Porphyrias Consortium
- Primary Immune Deficiency Treatment Consortium
- Rare Kidney Stone Consortium
- Rare Lung Diseases Consortium
- Rett Syndrome, MECP2 Duplications and Rett-Related Disorders Natural History
- Sterol and Isoprenoid Research Consortium
- Urea Cycle Disorders Consortium
- Vasculitis Clinical Research Consortium

Detailed descriptions of the consortia and the DMCC can be found on the Consortia webpage.[2379]

NIH Funding for FY 2016, FY 2017, and FY 2018

The collaborations are made possible through awards by NIH, totaling about $29 million in FY 2018 funding alone, with approximately $1.25 million per consortium per FY.

In addition to NIH funding, PAGs also provide supplemental funds for many of the projects.

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Programmatic Activities and Outcomes

Examples of some RDCRN programmatic activities and outcomes in FY 2016, 2017, and 2018 are outlined below.

As an example of patient advocacy involvement in RDCRN, the American Partnership for Eosinophilic Disorders (APFED) is one of several PAGs collaborating with CEGIR to conduct research that is meaningful to the patient community. As part of CEGIR, one of APFED's primary responsibilities is educating the patient community about the work the consortium is accomplishing. A variety of multimedia, patient-friendly communication tools are utilized to reach out to patients, caregivers, and health care professionals, including internet-based platforms (e.g., the APFED website; monthly e-newsletters and quarterly membership newsletters; an online community, the Inspire™ network; and social media channels, such as Facebook and Twitter); presentations at annual conferences and regional workshops; and print materials distributed at medical society meetings and fundraising events and through the mail.

An example of cross-consortium activities in FY 2017 includes efforts to understand the mechanistic target of rapamycin (mTOR) pathway. It is becoming clear that problems with some basic cellular processes can contribute to diseases affecting different organs. One cellular signaling pathway that appears to be involved in multiple diseases is the mTOR pathway, which is central to cellular energy metabolism and

[2379] https://www.rarediseasesnetwork.org/about.

growth; thus, abnormal function of the mTOR pathway can contribute to disease processes in various organs. A cross-consortia effort was initiated to gather expertise in this cellular pathway and initiate pilot studies that benefit a large group of consortia. Discussions revealed an important gap in reliably measuring mTOR activity in peripheral blood mononuclear cells, a metric that could provide a potential biomarker of disease severity, as well as a measure of target engagement in treatment trials.

As an example of training and supporting the next generation of rare disease researchers, the RDCRN Conference on Clinical Research for Rare Diseases focuses on research methodology for rare diseases and is designed for trainees and junior faculty engaged in research in rare diseases. Among the conference speakers in 2018 were RDCRN investigators, FDA officials, biomedical industry experts, and PAG representatives. The meeting agenda in 2018 included the following topics: design issues for clinical trials of small sample sizes, systems biology and big data in rare diseases, working with FDA and industry for rare diseases research, novel approaches to rare diseases study design, and challenges and opportunities involved in developing an academic career studying rare diseases. A poster session allowed presentation of research in rare diseases, with informal review and comments provided by senior investigators and NIH program officials attending the meeting.

Research Activities and Outcomes

Examples of some RDCRN research activities and outcomes in FY 2016, 2017, and 2018 are outlined below.

A report from the Urea Cycle Disorders Consortium, *Improving Long Term Outcomes in Urea Cycle Disorders*, was released. The report summarizes the consortium findings related to outcome, focusing primarily on neuroimaging findings and neurocognitive function. Neuroimaging studies in late-onset ornithine transcarbamylase deficiency (OTCD) offered evidence that brain injury caused by biochemical dysregulation may impact neuroanatomy serving working memory processes, an important component of executive function and regulation. Intellectual manifestations in OTCD and other urea cycle disorders vary. However, when neuropsychological deficits occur, they tend to be more prominent in motor/performance areas on both intelligence tests and other measures. In some disorders, adults performed significantly less well than younger patients. Further longitudinal follow-up will reveal whether this is due to declines throughout life or to improvements in diagnostics (especially newborn screening) and treatments in the younger generation of patients.[2380]

A study published in FY 2017 suggests that analyzing levels of the protein p75ECD in urine samples from people with amyotrophic lateral sclerosis (ALS) may help monitor disease progression as well as determine the effectiveness of therapies. The study was conducted as part of the CReATe consortium within RDCRN.[2381]

RDCRN is also an example of Clinical Trial Readiness. NIH-Supported Research Helps Advance a Potential Rare Disease Gene Editing Treatment into Clinical Trials. The LDN supported research that helped to

[2380] Waisbren SE, et al. *J Inherit Metab Dis* 2016;39(4):573-84. PMID: 27215558.
[2381] Shepheard SR, et al. *Neurology* 2017;88(12):1137-43. PMID: 28228570.

overcome translational roadblocks by charting how several rare, inherited disorders progress in patients over time. Working with Sangamo researchers, principal investigator Chester Whitley, M.D., Ph.D., and LDN Fellow Li Ou, Ph.D., found that a gene-editing technique could prevent or reverse Hurler syndrome in some tissues in mice with the disease. When the researchers evaluated the technique's effects in a learning behavior test, the results in treated mice suggested that the therapy reached the brain. Along with similarly promising findings in mice with Hunter syndrome, the stage was set for the next step: testing in patients. Sangamo made headlines when scientists made the first attempt to edit a gene inside the human body in a patient with Hunter syndrome.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of RDCRN

Future Directions

The continued commitment of NCATS and the NIH ICs that collaborate with NCATS is a testament to the effectiveness of the principles of RDCRN. Many of RDCRN's novel practices have been adopted elsewhere, and the network's impact on the rare diseases community and rare diseases research is immense.

The fourth round of applications to the RDCRN consortia and the DMCC will be awarded in the summer of 2019. The focus of the upcoming cycle is clinical trial readiness, that is, addressing unmet needs that will move the research forward from its current state in a rigorous and swift manner toward trials and, ultimately, treatment.

The fourth round will also embrace NCATS' approach to translational science, which emphasizes recognition of the commonalities across diseases, including rare diseases. By identifying shared molecular biology, signaling pathways, and other common characteristics across several diseases at one time, researchers hope that results can be informative for multiple disorders simultaneously. This is one approach the NCATS is taking to transform how research is conducted to speed the translation of laboratory discovery to therapeutics in the clinic.

DMCC will be making significant changes in the fourth round, as well. It will be embracing the NIH Strategic Plan for Data Science, with an emphasis on FAIR data principles and a move toward common architecture, infrastructure, and tools to establish a platform for building resources for investigators and the research community to share.

Evaluation Plans

In 2018–2019, a comprehensive evaluation of the program was conducted, including means of data collection and management and the overall structure of the program. From this evaluation, modifications were made to the next round of RDCRN. The program will continue to be evaluate by data-driven metrics, NIH programmatic oversite, and an annual evaluation with recommendations by an External Scientific Panel.

Table 5. RDCRN Consortia Active Through FY 2018.

RDCRN Consortia	Cycle I 2003–2007	Cycle II 2008–2013	Cycle III 2014–2019
Vasculitis Clinical Research Consortium	X	X	X
Urea Cycle Disorders Consortium	X	X	X
Genetic Disorders of Mucociliary Clearance Consortium	X	X	X
Rett Syndrome, MECP2 Duplication and Rett Related Disorders (formerly Angelman, Rett & Prader-Willi Consortium)	X	X	X
Clinical Investigation of Neurologic Channelopathies	X		
Rare Genetic Steroid Disorders	X		
Rare Thrombotic Diseases Consortium	X		
Cholestatic Liver Disease Consortium	X		
Bone Marrow Failure Consortium	X		
Sterol and Isoprenoid Research Consortium		X	X
Autonomic Disorders Consortium		X	X
Rare Kidney Stone Consortium		X	X
Nephrotic Syndrome Study Network		X	X
Primary Immune Deficiency Treatment Consortium		X	X
Prophyrias Consortium		X	X
Brain Vascular Malformations Consortium		X	X
Inherited Neuropathies Consortium		X	X
Lysosomal Disease Network		X	X
Dystonia Coalition		X	X
North American Mitochondrial Disease Consortium		X	X
Salivary Gland Carcinomas Consortium		X	
Chronic Graft Versus Host Disease		X	
Brittle Bone Disorders Consortium			X
Consortium of Eosinophilic Gastrointestinal Disease Research			X
Rare Lung Disease Consortium	X		X
Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium			X
Developmental Synatopathies Consortium			X

Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium			X
Data Management and Coordination Center	X	X	X

Autism Centers of Excellence

Establishment of the Autism Centers of Excellence

According to CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, about 1 in 59 8-year-old children has ASD.[2382] These estimates are based on data collected from health and special education records of children living in 11 areas of the U.S. during 2014. NIH is working to better understand the causes of ASD and to develop treatments for this serious and disabling disorder.

To expand the public health response to the challenges posed by ASD, Congress passed the *Combating Autism Act of 2006*, aimed at expanding research and improving coordination among public health research agencies, including NIH. The *Combating Autism Act* reauthorized the Interagency Autism Coordinating Committee (IACC), a federal advisory committee designed to coordinate agency activities and identify priority areas in an annual Strategic Plan for ASD Research. As part of its response to the *Combating Autism Act*, NIH formed the Autism Centers of Excellence (ACE) program by consolidating two previous ASD research programs—the Collaborative Programs of Excellence in Autism (established in 1997) and Studies to Advance Autism Research and Treatment (established in 2002 and completed in 2008)—into a single research effort.

Most recently, Congress reauthorized these federal ASD activities (including the ACE program and the IACC) through the *Autism Collaboration, Accountability, Research, Education, and Support Act of 2014* (the *Autism CARES Act*, P.L. 113-157), which was signed into law August 2014. The *Autism CARES Act* re-emphasized the coordination of federal activities and added specific direction to focus on the importance of the transition to adulthood for youth with autism. In addition, the Act required the appointment of an official within HHS to ensure accountability and implementation of autism-related activities across HHS. The *Autism CARES Act* expires September 2019.

How the Autism Centers of Excellence Function Within the NIH Framework

The goals of the ACE program were established by the NIH Autism Coordinating Committee (ACC), a working group composed of representatives from NIH Institutes that support the largest share of NIH's ASD research. The ACC is tasked with enhancing the quality, pace, and coordination of research efforts at NIH and monitoring scientific progress on an ongoing basis. The five current ACC member Institutes

[2382] Baio J, et al. *MMWR Surveill Summ* 2018;April 27;67(6):1-23.

(NICHD, NIDCD, NIEHS, NIMH, and NINDS) provide funding to the ACE program and share administrative and oversight responsibilities.

The ACE program, which is informed by the Strategic Plan for ASD developed and updated by IACC, serves as a flagship initiative for NIH's autism research portfolio. ACE grants enable large-scale center and network projects that could not be supported through a typical NIH grant.

The initial ACE program, funding for which began in FY 2007 and FY 2008, focused on identifying the causes of ASD and developing new and improved treatments. The second iteration of the ACE program, launched in FY 2012, focused on possible causes of ASD, risk and resilience in ASD, children with ASD who have limited speech and communication, preventive interventions and improved treatment, ASD among girls and women, and how genetic and environmental factors are associated with the development of ASD. In 2017, the ACE program began its third funding cycle. Research plan priority areas addressed through the current ACE program include research on biomarkers, genetic susceptibility, pharmacological treatments, early intervention, and risk and protective factors.

The ACE program comprises both centers and research networks. ACE centers foster multidisciplinary collaboration among teams of specialists at a single facility to address an interrelated set of research questions. Each center conducts interdependent subprojects. ACE networks unite researchers at many different facilities throughout the country; working as a unit, each network addresses a particular research question in depth. NIH currently funds five ACE research center grants and five ACE research network grants (see Table 6).

Description of Disease or Condition

Leo Kanner first described autism in 1943 as a disorder "characterized by extreme aloneness and a desire for the preservation of sameness, with a variety of behavioral (cognitive, affective) symptoms derived from them."[2383] Over time, growing recognition of a broader range of related disorders led to the use of the term *autism spectrum disorder,* which includes several complex neurodevelopmental disorders of early childhood that vary in severity, share common clinical features, and usually persist throughout the lifetime of the individual. Common features include social impairments; verbal and nonverbal communication difficulties; and restricted, repetitive, and/or stereotyped behavior patterns.

A child's primary caregivers are often the first to identify ASD symptoms. As early as infancy, a baby with ASD may be unresponsive to people or focus intently on one item to the exclusion of others for long periods. A child with ASD may appear to develop normally and then withdraw and become indifferent to social engagement. Clinicians can make a reliable ASD diagnosis for most children by age 3. The current ASD diagnostic criteria and classifications represent progress in identifying a core set of developmental symptoms that, in the past, clinicians might have diagnosed differently because the criteria for ASD were more narrowly defined than they are today.

[2383] Kanner L. *Nerv Child.* 1943;2:217-50.

Burden of Illness

The socioeconomic impact of ASD for families and society at large is tremendous. Although ASD varies greatly in character and severity, it occurs in all ethnic and socioeconomic groups and affects every age group. Currently, no coherent and comprehensive system of care is available for affected individuals. People with ASD may receive private and public services in special education settings, hospitals, university medical centers, or residential treatment facilities, among others.

Scientists and economists have estimated that the annual cost of providing care for all Americans with ASD is between $34 billion and $236 billion.[2384,2385] The estimated costs over a lifetime for each person can total $1.4 million to $3 million.[2386,2387] Families often incur large debts for medical and education services that public programs or medical insurance do not cover. In addition, ASD often leads to profound emotional hardships for patients and their families.

Estimates of the prevalence of ASD—the number of affected individuals at a given point in time—have increased markedly since the early 1990s. CDC currently estimates that as many as 1 in 59 8-year-old children has ASD. Boys are approximately four times as likely as girls to have ASD.[2388] However, it is unclear whether incidence—the number of new cases across time in the same population—has also increased. It is also unclear whether the rise in prevalence is due to such factors as the use of different criteria to diagnose ASD; earlier and more accurate ASD diagnoses; or increases in biologic, environmental, or other risk factors. A similar increase in ASD prevalence has occurred in other countries.

Scope of NIH Activities: Research and Programmatic

The centers and networks that make up the ACE program cover a broad range of ASD research areas, including early brain development and functioning, social interactions in infants, rare genetic variants and mutations, associations between autism-related genes and physical traits, underrepresented populations with ASD (such as women and girls and African Americans), and potential new treatments.

To support and accelerate research in the causes, diagnosis, and treatment of ASD, NIH created the National Database for Autism Research (NDAR), an informatics system and central data repository. The database collects a wide range of human subjects data—including phenotypic, clinical, and genomic data, as well as de-identified medical images—from individuals who participate in ASD research, regardless of the source of research funding. NDAR provides the infrastructure to store, search across, retrieve, and analyze these varied types of data. Although NDAR receives data from many publicly and privately funded research sources, all ACE centers and networks are expected to contribute their data to NDAR. NDAR is

[2384] Ganz ML. *Arch Pediatr Adolesc Med.* 2007;161(4):343-9. PMID: 17404130.
[2385] Buescher AV, et al. *JAMA Pediatr* 2014;168(8):721-8. PMID: 24911948.
[2386] Ganz ML. *Arch Pediatr Adolesc Med* 2007;161(4):343-9. PMID: 17404130.
[2387] Buescher AV, et al. *JAMA Pediatr* 2014;168(8):721-8. PMID: 24911948.
[2388] https://www.cdc.gov/mmwr/volumes/67/ss/ss6706a1.htm.

part of the NIMH Data Archive (NDA), which makes available human subjects data collected from hundreds of research projects across many scientific domains.

NIH Funding for FY 2016, FY 2017, and FY 2018

Five NIH Institutes fund the ACE program: NICHD, NIDCD, NIEHS, NIMH, and NINDS. NIH funding for the ACE program, which currently includes five research centers and five research networks, was $20.94 million in FY 2016, $25.99 million in FY 2017, and $21.46 million in FY 2018.[2389]

FY 2016, FY 2017, and FY 2018 Progress Report

Programmatic and Research Activities and Outcomes

The centers and networks that make up the ACE program cover a broad range of ASD research areas, including early brain development and functioning, social interactions in infants, rare genetic variants and mutations, associations between autism-related genes and physical traits, possible environmental risk factors and biomarkers, minimally verbal children, underrepresented populations with ASD (such as women and girls and African Americans), and potential new treatments.

The activities and accomplishments of the ACE program—including those centers and networks that received support in the first round of funding (FY 2007), those that were funded in the second round (FY 2012), and those that were awarded in the third round (FY 2017)—are highlighted briefly below (see also Table 6).

Table 6. Autism Centers of Excellence (ACEs).

Institution and Location	Year Started		
	First Round	Second Round	Third Round
University of California, Davis, CA (1)	2007	—	—
University of California, Davis, CA (2)	—	2013	—
University of California, Davis, CA (3)	—	—	2017
University of California, Los Angeles, CA (1)	2007	2012	2017
University of California, Los Angeles, CA (2)	2008	2013	2018
University of California, Los Angeles, CA (3)	—	2012	—
University of California, San Diego, CA	2007	—	—
University of Illinois, Chicago, IL	2007	—	—

[2389] NIH RePORT, accessed June 12, 2019. https://report.nih.gov/.

Institution and Location	Year Started		
	First Round	Second Round	Third Round
The University of North Carolina, Chapel Hill, NC (1)	2007	2012	2017
The University of North Carolina, Chapel Hill, NC (2)	—	2012	—
University of Pittsburgh, Pittsburgh, PA	2007	—	—
University of Washington, Seattle, WA	2007	—	—
Yale University, New Haven, CT	2008	2012	2017
Wayne State University, Detroit, MI	2008	—	—
Drexel University, Philadelphia, PA	2008	—	2017
Boston University, Boston, MA	—	2012	—
Emory University, Atlanta, GA	—	2012	2017
Boston Children's Hospital/Harvard Medical School, Boston, MA	—	2012	—
Mount Sinai School of Medicine, New York City, NY	—	2012	—
Duke University, Durham, NC	—	—	2017
The George Washington University, Washington, DC	—	—	2017
Florida State University, Tallahassee, FL	—	—	2017

ACE Centers and Networks Active During FY 2016–FY 2018

- UCLA (*P50HD055784, 2007–2022):* Over the last decade, researchers at this UCLA-based ACE center have made significant advances in the field, identifying risk genes, candidate brain-based biomarkers of treatment response and early risk markers of ASD beginning in the first few weeks of life. They developed new interventions for toddlers with social communication delays, identified a promising intervention to address repetitive behaviors, and showed how symptoms of ASD may be affected by connections between the thalamus, a part of the brain that generally regulates input from the senses to different parts of the brain, and the amygdala, which helps to process emotions.[2390] In the current funding cycle, scientists aim to (1) determine how differences in genetic risk for autism affect early brain development, neuroimaging, and electroencephalography (EEG) biomarkers in the first year of life; (2) examine heterogeneity in treatment response using an adaptive treatment intervention for very young children at risk for ASD; (3) use MRI in youth with ASD to determine how behavioral differences and genetic risk

[2390] Green SA, et al. *Autism Res* 2017;10(5):801-9. PMID 27896947.

differentially affect brain activation and structural and functional connectivity; and (4) conduct an early-stage pharmacological study aimed to increase social interest and social reward responsivity in adolescents and young adults enrolled in a social skills intervention.

- UCLA *(R01MH081754, 2008–2013; R01MH100027, 2013–2023):* Researchers in this UCLA-based research network have been utilizing large genomic databases to investigate how rare genetic variations, mutations, and abnormalities affect an individual's risk for autism. Their findings show that while common variations in genetic mutation at the individual level contribute less to a person's risk for autism,[2391] common inherited variants or mutations at the family level exert stronger effects on ASD risk.[2392] The ACE scientists have recruited a large number of research subjects with self-reported African ancestry (African Americans), an important population that has not previously been well represented in ASD genetics. These researchers reported that in families with multiple affected individuals, a substantial contribution to ASD risk comes from inherited rare variations.[2393] The researchers also identified several likely pathogenic de novo rare mutations in their African American cohort, including in known ASD risk genes, and found that ASD polygenic risk scores derived from European populations perform poorly when applied to the African American cohort. In the current funding cycle, the scientists aim to increase the size of this cohort.
- The University of North Carolina at Chapel Hill *(R01HD055741, 2007–2022):* Researchers from this ACE network are studying abnormal processes in early brain development by examining images of the brains of very young children at risk for developing ASD because they have an older sibling with autism. An early study from this network found evidence of enlarged portions of the amygdala in 6- to 7-year-old children with ASD and showed that these differences were associated with deficits in social and communicative behavior.[2394] A brain imaging study from this group showed early brain changes in infants with a high family risk of developing autism, as well as a computer program that identified a majority of infants who later developed autism.[2395] Another brain imaging study characterized the development of white-matter circuitry, or the connections formed in the brain, for infants with fragile X syndrome, the most common inherited cause of intellectual disability in males, which has been associated with ASD. In the current funding period, the researchers will follow these children through ages 7 to 10 years to determine how their brains change as they grow and the potential effects of ASD on learning and social development. Based on what they learn, they aim to develop interventions tailored to school-age children with ASD.
- Yale University and The George Washington University *(R01MH100028, 2012–2022):* This ACE network is investigating the underexamined issue of ASD in women and girls. The project will study a larger sample of girls with autism than has been studied previously, focusing on genes, brain function, and behavior throughout childhood and adolescence. The objectives are to identify causes of ASD and develop new treatments. By following children through adolescence

[2391] Anney R, et al. *Hum Mol Genet* 2012;21(21):4781-92. PMID: 22843504.
[2392] Gaugler T, et al. *Nat Genet* 2014;46(8):881-5. PMID: 25038753.
[2393] Leppa VM, et al. *Am J Hum Genet* 2016;99(3):540 PMID: 27569545.
[2394] Kim JE, et al. *Arch Gen Psychiatry* 2010;67(11):1187-97. PMID: 21041620.
[2395] Hazlett HC, et al. *Nature* 2017;542(7641):348-51. PMID: 28202961.

and into adulthood, the scientists hope to identify differences between boys and girls related to ASD risk and how they respond to interventions. The researchers also aim to uncover information that will help males and females living with ASD better manage the transition to adulthood.

- Emory University *(P50MH100029, 2012–2022):* The team of researchers at the Emory ACE is studying risk and resilience in ASD, with particular interest in factors that lead to positive outcomes or social disability. The team is also conducting randomized clinical trials to develop treatments for 12-month-old children. The center will follow hundreds of infants from birth to 30 months, including those at high risk for ASD. Previously, the group showed that, when looking at videos of people speaking, infants who were later diagnosed with ASD had eye movements that differed from those of typically developing infants.[2396] More recently, the group found a genetic basis for those eye movements.[2397]
- Florida State University *(R01HD093055, 2017–2022):* Researchers in the Florida State University–based network are testing a two-part intervention designed to empower parents of children with ASD. The researchers are offering parents problem-solving education in a six-session intervention to help them access the services their children need and to adapt to caring for a child with special needs. Parents also receive training in early social interaction, which teaches them to support their children's communication and social skills in everyday routines, activities and settings.
- Duke University *(P50HD093074, 2017–2022):* An estimated 40 to 60 percent of people with ASD have attention deficit hyperactivity disorder (ADHD), which encompasses such symptoms as difficulty paying attention, problems controlling behavior, and hyperactivity. Scientists at this Duke University center are examining how ADHD may influence the diagnosis and treatment of autism and plan to observe children who have ASD alone, ASD and ADHD, and ADHD alone and compare them to typically developing children. They are testing whether the stimulant medication used to treat ADHD will help children with both conditions. This group has also demonstrated that automated computer vision analysis can detect atypical attention behaviors in toddlers with ASD.
- University of California, Davis *(P50HD093079, 2017–2022):* Researchers at this center continue their efforts to classify children into different subgroups, based on their symptoms, behavioral characteristics, and genetic features and aim to develop behavioral and drug interventions appropriate for each subtype. The researchers have found that by age 3, about 15 percent of boys with ASD have brains that are unusually large relative to the size of their bodies. These boys have a higher rate of regression, or loss of social and communications skills, and are more likely to have an intellectual disability. In contrast, at age 3, only 3 percent of girls with ASD had disproportionately large brains. The researchers plan to follow these children through childhood to determine whether the structure of their brains differ from those of typically developing children.
- Yale University *(P50MH115716, 2017–2022):* Researchers at this Yale center are investigating brain connections in fetuses and newborns to identify early indicators of ASD. They are also examining whether boys and girls with ASD differ in their brain circuitry, with the aim of improving

[2396] Jones W, Klin A. *Nature* 2013;504(7480):427-31. PMID: 24196715.
[2397] Constantino JN, et al. *Nature* 2017;547(7663):340-4. PMID: 28700580.

diagnosis and treatment. In addition, they are evaluating an intervention to improve social functioning in children at high risk for ASD.

- Drexel University *(R01MH115715, 2017–2022):* Investigators in the ACE network based out of Drexel University are evaluating autism screening for all toddlers. They are conducting a randomized, controlled trial of 8,000 toddlers to determine whether screening lowers the average age of ASD diagnosis, leads to earlier interventions, and improves outcomes.
- Boston Children's Hospital/Harvard Medical School *(U01NS082320, 2012–2019):* This network studied individuals with tuberous sclerosis complex (TSC), a rare genetic disease that causes tumors in the brain and other vital organs.[2398] People with TSC have an increased risk for both autism and epilepsy. Researchers used brain imaging and EEG to track brain development in infants with TSC. They found that early seizure onset negatively impacts neurodevelopment in TSC and that EEG can predict which infants are at risk for developing epilepsy.[2399] Based on these findings, an ongoing NIH-funded clinical trial will assess whether early treatment with vigabatrin, an antiseizure medication, will improve neurocognitive outcomes in infants with TSC.[2400]
- Boston University *(P50DC013027, 2012–2019):* Researchers at this ACE studied ASD in children with limited speech and used brain-imaging technologies in an effort to understand why certain children with ASD do not learn to speak, with the goal of helping them overcome this limitation. The research team also tested new approaches to help young children with ASD acquire language.
- University of California, Davis *(R01MH100030, 2013–2019)*: Researchers at this network have been conducting two controlled trials to (1) identify the effects of intensity and delivery style on developmental progress of toddlers with ASD and (2) determine whether toddlers from a previous trial of a specific intervention approach, the Early Start Denver Model, maintain positive effects of treatment after 3 years.
- UCLA *(R01HD073975, 2012–2019):* This UCLA network has focused on developing and testing intensive interventions for minimally verbal children with ASD; these interventions are designed to optimize the number of unique socially communicative and unique spoken words. Scientists hope this translational research will identify new intervention mechanisms for nonverbal children with autism.
- Mount Sinai School of Medicine *(U01HD073978, 2012–2018):* These ACE network investigators are conducting a critical study to understand how genetic and environmental factors influence the development of autism. The team of American and international researchers is analyzing detailed records and biospecimens from 4.5 million births involving 20,000 cases of ASD from seven countries (the U.S., Australia, Denmark, Finland, Israel, Norway, and Sweden). The analysis will span three generations and involve grandparents, parents, aunts, uncles, siblings, and cousins.
- The University of North Carolina at Chapel Hill and Duke University *(U01HD073984, 2012–2017):* The second ACE network at the University of North Carolina tested whether treatments with oxytocin nasal spray could improve social interaction and communication in children with ASD.

[2398] https://www.ninds.nih.gov/Disorders/All-Disorders/Tuberous-Sclerosis-Information-Page.
[2399] Wu JY, et al. *Pediatr Neurol*. 2016;54:29-34. PMID: 26498039.
[2400] https://clinicaltrials.gov/ct2/show/NCT02849457.

Oxytocin is a neuropeptide used by brain cells to communicate and has been associated with social behaviors.

- Wayne State University *(U01NS061264, 2008–2016):* Investigators with the Wayne State network sites conducted a clinical trial to test the safety and efficacy of buspirone, a drug that targets one type of receptor for serotonin—one of several neurotransmitters that brain cells use to communicate with each other—as an early intervention in children with ASD under age 6. The trial showed that low-dose buspirone treatment in young children with ASD did not alter overall symptoms of autism. However, analysis of secondary outcome measures showed significant improvement in repetitive and restricted behaviors. The investigators suggest that further research could explore the use of buspirone as an adjunct therapy to target restrictive and repetitive behavior, in combination with other early interventions to address additional ASD symptoms.[2401]

ACE Centers and Networks with Funding That Ended Before FY 2016

- Drexel University *(R01ES016443, 2008–2015):* Researchers with the Drexel University network studied possible risk factors and biological indicators of ASD before and soon after birth, as part of the larger Early Autism Risk Longitudinal Investigation effort.
- University of Pittsburgh *(P50HD055748, 2007–2014):* The University of Pittsburgh ACE studied how people with ASD learn and understand information. Researchers compared information processing, emotional regulation, and brain connectivity in infant siblings; first-diagnosed toddlers with autism; and groups of children, adolescents, and adults with and without autism.
- University of Illinois at Chicago *(P50HD055751, 2007–2014):* Researchers studied genetic factors, brain chemicals, and brain functions that could account for repetitive behaviors in people with ASD. They also tested whether genetic differences influence how individuals respond to certain medications intended to reduce the frequency of these behaviors.
- University of California, San Diego *(P50MH081755, 2007–2014):* Building on earlier studies linking brain development to the risk of autism, these ACE investigators showed how patches of disorganization in neuronal cells in the prefrontal cortex of children with ASD were traced back to prenatal development. Both the nature of the cellular disorganization and its specific location in the prefrontal cortex provide more precise targets for researchers to examine potential causes of and treatments for ASD.[2402]
- Yale University *(P50MH081756, 2008–2014):* Researchers conducted studies to search for biomarkers of visual engagement and auditory perception in infants at risk for ASD. Working with collaborators from Emory University, scientists from the Yale University ACE found that focus on eyes was lower among 2- to 6-month-old infants later diagnosed with ASD than in children with typical development. Results from another center study showed that, when viewing significant visual information, such as caregiver faces or peer interaction, typically developing children inhibited eye-blinking earlier than infants who were diagnosed with ASD.[2403]

[2401] Chugani DC, et al. *J Pediatr.* 2016;170:45-53. PMID: 26746121.
[2402] Stoner R, et al. *N Engl J Med* 2014;370(13):1209-19. PMID: 24670167.
[2403] Shultz S, et al. *Proc Natl Acad Sci USA* 2011;108(52):21270-5. PMID: 22160686.

- University of Washington *(P50HD055782, 2007–2013).* Researchers investigated genetic and other factors that might increase a person's risk for ASD and factors that might protect people from developing ASD. Researchers at the University of Washington ACE also conducted a randomized computerized training program for adults with ASD who showed initial impairment in their ability to recognize faces. The results suggest that adults with ASD who undergo the computerized training can improve their facial recognition and processing skills.[2404]
- University of California, Davis *(R01MH081757, 2007–2013):* Findings from this ACE showed that starting children with signs of ASD on interventions at an early age and providing more hours of intervention were more critical for improvements in behavior and development than whether the interventions were implemented by parents or in community settings.[2405] However, another study demonstrated that a parent-implemented version of the Early Start Denver Model intervention was more effective at reducing parents' stress related to a child's autism diagnosis and improving parents' sense of personal competence than participation in a regular community-provided intervention program.[2406] This group also used MRI images to show that high-risk infants who were later diagnosed with ASD had abnormally high volumes of cerebrospinal fluid, which cushions the brain and spinal cord.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the ACE Program

Evaluation Plans

The *Combating Autism Act of 2006* and the *NIH Reform Act of 2006* require that NIH conduct periodic reviews of the ACE program. To implement this requirement, NIH formed the Autism Evaluation Implementation Oversight (AEIO) working group, comprising Planning and Evaluation Officers at the five NIH Institutes (NICHD, NIDCD, NIEHS, NIMH, and NINDS) that provide financial support and scientific expertise to the ACE program.

Between 2013 and 2015, the AEIO working group continued to gather data to assess the implementation and outputs of the ACE program during its intermediate phase, from 2010 through 2014. The findings on research, training, and dissemination activities of the ACE centers and networks, as well as research collaborations and community partnerships, were similar to data in the earlier ACE process evaluation.

The ACE centers and networks have continued to form and participate in partnerships with a variety of public and private organizations, including advocacy groups, pharmaceutical companies, federal agencies, and others. The program is building research capacity in the field by training postdoctoral and early-career researchers. Data from this program have been shared with the research community through several accessible databases, including NDAR, Autism Brain Imaging Data Exchange, Marcus Autism Center Vocal,

[2404] Faja S, et al. *J Autism Dev Disord* 2012;42(2):278-93. PMID: 21484517.
[2405] Rogers SJ, et al. *J Am Acad Child Adolesc Psychiatry.* 2012;51(10):1052-65. PMID: 23021480.
[2406] Estes A, et al. *J Autism Dev Disord* 2014;44(2):353-65. PMID: 23838727.

Autism Speaks Baby Sibs Research Consortium, Autism Genetic Research Exchange, NIMH Repository and Genomics Resource, NLM/NCBI genetic and gene expression data, and NIH Genetics Repository. Scientific findings have been disseminated across numerous venues, including grantee meetings, scientific conferences, workshops and trainings, websites, community forums, press releases, fact sheets and pamphlets, testimony and briefings to legislators, and mass media publications.

Future Directions

NIH convenes an annual, 2-day meeting during which investigators present progress toward the goals of their ACE and exchange ideas for collaborations. ACE principal investigators and project principal investigators, as well as core directors and data managers, attend. Principal investigators are encouraged to invite K award (career development grant) recipients, fellows, and postdoctoral students from their laboratories.

Appendix A:
Excerpts of Legal Authorities Related to the NIH Director's Triennial Report to Congress

***PUBLIC HEALTH SERVICE ACT* APPOINTMENT AND AUTHORITY OF DIRECTOR OF NIH SECTION 402**(b) In carrying out the purposes of section 301, the Secretary, acting through the Director of NIH—(7)(A) shall, through the Division of Program Coordination, Planning, and Strategic Initiatives—(ii) include information on such research in reports under section 403.

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TRANS-NIH RESEARCH REPORTING
SECTION 402A(c)(2)(B) REPORTING.—Not later than 2 years after the date of enactment of the *21st Century Cures Act*, the head of each national research institute or national center shall submit to the Director of the National Institutes of Health a report, to be included in the triennial report under section 403, on the amount made available by the institute or center for conducting or supporting research that involves collaboration between the institute or center and 1 or more other national research institutes or national centers.

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TRIENNIAL REPORTS OF DIRECTOR OF NIH
SECTION 403(a) IN GENERAL.—The Director of NIH shall submit to the Congress on a triennial basis a report in accordance with this section. The first report shall be submitted not later than 1 year after the date of the enactment of the *National Institutes of Health Reform Act of 2006*. Each such report shall include the following information:

(1) An assessment of the state of biomedical and behavioral research.
(2) A description of the activities conducted or supported by the agencies of the National Institutes of Health and policies respecting the programs of such agencies.
(3) A description of intra-National Institutes of Health activities, including—
    (A) identification of the percentage of funds made available by each national research institute and national center with respect to each applicable fiscal year for conducting or supporting research that involves collaboration between the institute or center and 1 or more other national research institutes or national centers; and
    (B) recommendations for promoting coordination of information among the centers of excellence.
(4) A catalog of all the research activities of the agencies, prepared in accordance with the following:
    (A) The catalog shall, for each such activity—
        (i) identify the agency or agencies involved;
        (ii) state whether the activity was carried out directly by the agencies or was supported by the agencies and describe to what extent the agency was involved;

and

(iii) identify whether the activity was carried out through a center of excellence.

(B) In the case of clinical research, the catalog shall, as appropriate, identify study populations by demographic variables, including biological and social variables and relevant age categories (such as pediatric subgroups), and determinants of health, that contribute to research on minority health and health disparities.

(C) Research activities listed in the catalog shall include, where applicable, the following:

(i) Epidemiological studies and longitudinal studies.

(ii) Disease registries, information clearinghouses, and other data systems.

(iii) Public education and information campaigns.

(iv) Training activities, including—

(I) National Research Service Awards and Clinical Transformation Science Awards;

(II) graduate medical education programs, including information on the number and type of graduate degrees awarded during the period in which the programs received funding under this title;

(III) investigator-initiated awards for postdoctoral training and postdoctoral training funded through research grants;

(IV) a breakdown by demographic variables and other appropriate categories; and

(V) an evaluation and comparison of outcomes and effectiveness of various training programs.

(v) Clinical trials, including a breakdown of participation by study populations and demographic variables, including relevant age categories (such as pediatric subgroups), information submitted by each national research institute and national center to the Director of National Institutes of Health under section 492B(f), and such other information as may be necessary to demonstrate compliance with section 492B and other applicable requirements regarding inclusion of demographic groups.

(vi) Translational research activities with other agencies of the Public Health Service.

(5) A summary of the research activities throughout the agencies, which summary shall be organized by the following categories, where applicable:

(A) Cancer.

(B) Neurosciences.

(C) Life stages, human development, and rehabilitation.

(D) Organ systems.

(E) Autoimmune diseases.

(F) Genomics.

(G) Molecular biology and basic science.

(H) Technology development.

(I) Chronic diseases, including pain and palliative care.

(J) Infectious diseases and bioterrorism.

(K) Minority health and health disparities.

(L) Such additional categories as the Director determines to be appropriate.

(6) A review of each entity receiving funding under this title in its capacity as a center of excellence (in this paragraph referred to as a “center of excellence”), including the following—

(A) An evaluation of the performance and research outcomes of each center of excellence.

(B) Recommendations for improving the effectiveness, efficiency, and outcomes of the centers of excellence.

(b) REQUIREMENT REGARDING DISEASE-SPECIFIC RESEARCH ACTIVITIES.—In a report under subsection (a), the Director of NIH, when reporting on research activities relating to a specific disease, disorder, or other adverse health condition, shall—

(1) present information in a standardized format;
(2) identify the actual dollar amounts obligated for such activities; and
(3) include a plan for research on the specific disease, disorder, or other adverse health condition, including a statement of objectives regarding the research, the means for achieving the objectives, a date by which the objectives are expected to be achieved, and justifications for revisions to the plan.

(c) ADDITIONAL REPORTS.—In addition to reports required by subsections (a) and (b), the Director of NIH or the head of a national research institute or national center may submit to the Congress such additional reports as the Director or the head of such institute or center determines to be appropriate.

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SCIENTIFIC FRAMEWORK FOR RECALCITRANT CANCERS
SECTION 417G
(d) REPORTING.—

(1) BIENNIAL REPORTS.—The Director of NIH shall ensure each biennial[1] report under section 403 includes information on actions undertaken to carry out each scientific framework developed under subsection (a) with respect to a recalcitrant cancer, including the following:
    (A) Information on research grants awarded by the National Institutes of Health for research relating to such cancer.
    (B) An assessment of the progress made in improving outcomes (including relative survival rates) for individuals diagnosed with such cancer.
    (C) An update on activities pertaining to such cancer under the authority of section 413(b)(7).

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OFFICE OF RESEARCH ON WOMEN'S HEALTH
SECTION 486(d)(5) ADVISORY COMMITTEE.—

(A) The Advisory Committee shall prepare a biennial report describing the activities of the Committee, including findings made by the Committee regarding—
    (i) compliance with section 492B;
    (ii) the extent of expenditures made for research on women's health by the agencies of the National Institutes of Health; and
    (iii) the level of funding needed for such research.
(B) The report required in subparagraph (A) shall be submitted to the Director of NIH for inclusion in the report required in section 403.

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[1] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

BIENNIAL REPORT

SECTION 486B(a) IN GENERAL.—With respect to research on women's health, the Director of the Office shall, not later than February 1, 1994, and biennially thereafter, prepare a report—

(1) describing and evaluating the progress made during the preceding 2 fiscal years in research and treatment conducted or supported by the National Institutes of Health;
(2) describing and analyzing the professional status of women physicians and scientists of such Institutes, including the identification of problems and barriers regarding advancements;
(3) summarizing and analyzing expenditures made by the agencies of such Institutes (and by such Office) during the preceding 2 fiscal years; and
(4) making such recommendations for legislative and administrative initiatives as the Director of the Office determines to be appropriate.

(b) INCLUSION IN BIENNIAL[2] REPORT OF DIRECTOR OF NIH.—The Director of the Office shall submit each report prepared under subsection (a) to the Director of NIH for inclusion in the report submitted to the President and the Congress under section 403.

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INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

SECTION 492B(f) REPORTS BY ADVISORY COUNCILS.—The advisory council of each national research institute shall prepare triennial reports describing the manner in which the institute has complied with this section. Each such report shall be submitted to the Director of the institute involved for inclusion in the triennial report under section 403.

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HUNTER KELLY RESEARCH PROGRAM

SECTION 1116(c) REPORTS.—The Director is encouraged to include information about the activities carried out under this section in the biennial[3] report required under section 403. If such information is included, the Director shall make such information available to be included on the Internet Clearinghouse established under section 1112.

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MICROBICIDE RESEARCH

SECTION 2351A(a) FEDERAL STRATEGIC PLAN.—The Director of the Office shall—

(1) expedite the implementation of the Federal strategic plans required by section 403(a) of the *Public Health Service Act* (42 U.S.C. 283(a)(5)) regarding the conduct and support of research on, and development of, a microbicide to prevent the transmission of the human immunodeficiency virus; and
(2) review and, as appropriate, revise such plan to prioritize funding and activities relative to their scientific urgency and potential market readiness.

[2] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

[3] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

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***NATIONAL INSTITUTES OF HEALTH REFORM ACT OF 2006*, P.L. 109-482**

ENHANCING THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD
SECTION 106 (codified as a note in 42 USC 284)
(a) IN GENERAL.—In administering the Clinical and Translational Science Award, the Director of NIH shall establish a mechanism to preserve independent funding and infrastructure for pediatric clinical research centers by—

(1) allowing the appointment of a secondary principal investigator under a single Clinical and Translational Science Award, such that a pediatric principal investigator may be appointed with direct authority over a separate budget and infrastructure for pediatric clinical research; or
(2) otherwise securing institutional independence of pediatric clinical research centers with respect to finances, infrastructure, resources, and research agenda.

(b) REPORT.—As part of the biennial[4] report under section 403 of the *Public Health Service Act*, the Director of NIH shall provide an evaluation and comparison of outcomes and effectiveness of training programs under subsection (a).

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***21ST CENTURY CURES ACT*, P.L. 114-255**

EUREKA PRIZE COMPETITIONS
SECTION 2002 (codified in 42 USC 283q)
(b) TRACKING; REPORTING.—The Director of the National Institutes of Health shall—

(1) collect information on—
    (A) the effect of innovations funded through the prize competitions under this section in advancing biomedical science or improving health outcomes pursuant to subsection (a); and
    (B) the effect of the innovations on Federal expenditures; and
(2) include the information collected under paragraph (1) in the triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032).

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APPROPRIATE AGE GROUPINGS IN CLINICAL RESEARCH
SECTION 2038(i)(3) PUBLIC AVAILABILITY OF FINDINGS AND CONCLUSIONS.—The Director of the National Institutes of Health shall –

(A) make the findings and conclusions resulting from the workshop under paragraph (1) and updates to policies in accordance with paragraph (2), as applicable, available to the public on the Internet website of the National Institutes of Health; and
(B) ensure that age-related data reported in the triennial report under section 403 of the Public Health Service *Act* (42 U.S.C. 283) (as amended by section 2032) are made available to the public on the Internet website of the National Institutes of Health.

[4] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

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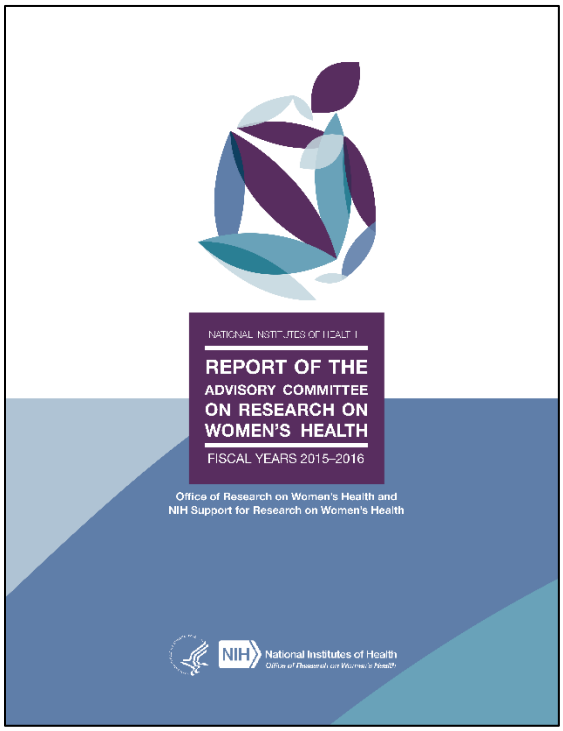
TICK-BORNE DISEASES

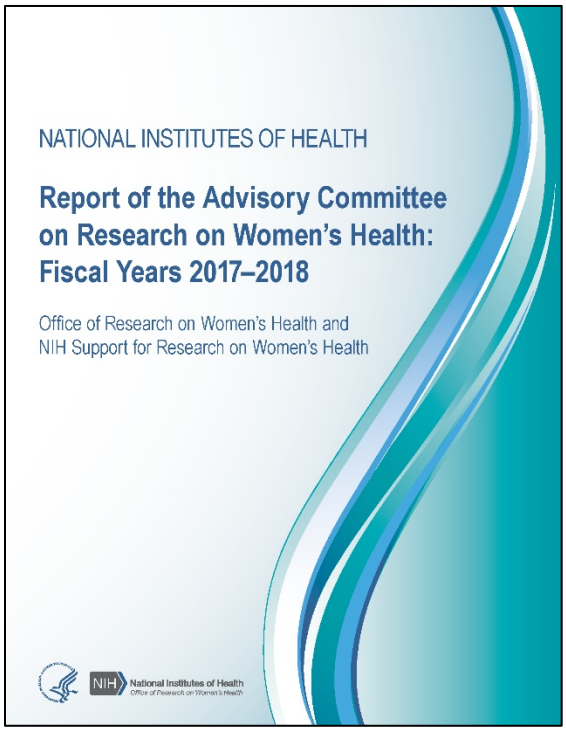
SECTION 2062(a) IN GENERAL.—The Secretary of Health and Human Services (referred to in this section as ''the Secretary'') shall continue to conduct or support epidemiological, basic, translational, and clinical research related to vector-borne diseases, including tick-borne diseases.

(b) REPORTS.—The Secretary shall ensure that each triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032) includes information on actions undertaken by the National Institutes of Health to carry out subsection (a) with respect to tick-borne diseases.

Appendix B:
Report of the Advisory Committee on Research on Women's Health

This report details the NIH-wide programs and accomplishments carried out in fulfillment of the ORWH core mission. The report also provides highlights from research on women's health and on the influence of sex and gender on health and disease supported by NIH ICs and the OD. In addition, it presents information on NIH budget allocations for women's health research. Finally, the report documents the inclusion of women and minorities in NIH-funded clinical research during fiscal years 2017–2018. For the full reports, please see: https://orwh.od.nih.gov/research/funded-research-and-programs/research-reports/biennial-report.





Appendix C:
Actions Undertaken to Conduct or Support Research Related to Vector-Borne Diseases

NIH conducts and supports a comprehensive research program to advance science and identify approaches to prevent, diagnose, and treat vector-borne diseases and to control the vectors that transmit these diseases to humans. During FY 2016–FY 2018, NIH committed between $546 million and $630 million each year to vector-borne disease research.[1] To satisfy legislative requirements included in the *21st Century Cures Act* (P.L. 114-255), NIH has developed the following report of epidemiological, fundamental, translational, and clinical research related to vector-borne diseases, including tickborne diseases (TBDs).[2] This report is not comprehensive, but rather provides a representative cross-section of vector-borne disease research supported by NIH. A comprehensive listing of vector-borne disease activities supported by NIH can be found on the NIH Research Portfolio Online Reporting Tools (RePORT) website.[3]

Background

Vectors, including insects and ticks, can transmit many infectious disease pathogens to people. Diseases spread by vectors like mosquitoes are a serious public health threat that account for approximately 17 percent of all infectious diseases, according to the World Health Organization (WHO).[4] Recent outbreaks of mosquito-transmitted such viruses as dengue, Zika, and chikungunya in the Americas attest to the importance of maintaining a foundation of research and development efforts to respond effectively to these emerging infectious diseases.

NIH continues to support basic and translational research into new vector management and transmission-prevention strategies. Fundamental investigations of mosquito chemical sensing—both taste and smell—have led to the identification of new ways to interfere with host-seeking and mating behaviors and novel compounds for mosquito repellents or attractants. New infection models also have been developed to

[1] https://report.nih.gov/categorical_spending.aspx.
[2] See Appendix A for language in the *Public Health Service Act*, as amended by the *21st Century Cures Act* (P.L. 114-255), that is relevant to these requirements.
[3] https://report.nih.gov/categorical_spending.aspx.
[4] https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases.

study the biology and transmission of, as well as countermeasures, for such TBDs as Powassan virus, which is endemic in parts of the U.S., and tickborne encephalitis.

NIH also supports basic, translational, and clinical research to understand the impact of vector-borne pathogens infection on the human host and how they cause disease. Basic research efforts seek to identify critical cellular and molecular pathways involved in disease pathogenesis, the human immune system response, and how signaling pathways that impact multiple organ systems can lead to common symptoms, such as arthritis or skin conditions.

TBDs, including Lyme disease and Rocky Mountain spotted fever, are the most common illnesses transmitted by arthropods (e.g., ticks, insects, and mites) in the U.S. In this country, more than 20 different disease-causing bacteria, viruses, and parasites are transmitted to humans by tick bites and many additional TBDs occur internationally. Most of these diseases were unknown 50 years ago, and several were discovered only in the past decade.[5–7]

The number of TBD cases reported to health officials understates the scope of the problem. Lyme disease is the most commonly reported vector-borne disease in the U.S. It is the fifth most commonly reported nationally notifiable infectious disease, with 30,000 cases reported annually,[8] and accounts for more than 80 percent of all reported TBD cases.[9] Studies by the Centers for Disease Control and Prevention (CDC) estimate that the actual number of cases in the U.S. may exceed reported cases 10-fold, approximating 300,000 cases of Lyme disease annually.[10]

The increase in vector-borne disease incidence in the U.S. represents a growing public health threat as new pathogens emerge and the geographic distributions of vectors change. Unlike infectious diseases that spread directly from person to person or through intermediate surface contact, vector-borne diseases are transmitted through a complex interplay of human hosts, pathogens, vectors, and animal reservoirs. Wild and domestic animals—including mammals, reptiles, and birds—are often important players in vector-borne pathogen survival, reproduction, and spread. NIH is committed to conducting and supporting research to better understand the biology of vectors, how they transmit diseases, and how they find and interact with human or animal hosts, with the goal of developing and improving strategies to prevent the transmission of these diseases to humans.

[5] Chowdri HR, et al. *Ann Intern Med.* 2013;159(1):21-7. PMID: 23817701.
[6] Kosoy OI, et al. *Emerg Infect Dis.* 2015;21(5):760-4. PMID: 25899080.
[7] Pritt BS, et al. *Lancet Infect Dis.* 2016; 16(5):556-64. PMID: 26856777.
[8] https://www.cdc.gov/lyme/datasurveillance/index.html
[9] https://www.cdc.gov/lyme/datasurveillance/index.html.
[10] https://www.cdc.gov/lyme/datasurveillance/index.html.

NIH Actions to Support Vector-Borne Disease Research

Research Updates

Chikungunya

Chikungunya virus (CHIKV) is usually transmitted to people via the bite of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes.[11] Viral reservoirs include humans, rodents, birds, monkeys, and other animals. CHIKV was discovered in Tanzania in 1952 and has caused numerous outbreaks of chikungunya, a severe, debilitating, febrile, arthritic disease prevalent in Africa and the Indian Ocean region. Early symptoms of chikungunya disease are similar to those of dengue, making differential diagnosis difficult early in the infection. Since 2013, CHIKV has spread rapidly into parts of Europe, the Caribbean Islands, and Central and South America. Mother-to-child transmission of CHIKV may occur at birth if the mother has CHIKV in her blood and can lead to severe neonatal infection. No licensed vaccines or therapeutics exist for this disease.

Epidemiological Research

- Assessed virus circulation and burden of disease of chikungunya and dengue in Kenya during inter-epidemic periods (NIAID)

Fundamental Research

- Identified the molecule MXRA8 on human and animal cells as a key to the entry of CHIKV into host cells (NIAID)

Translational Research

- Developed a preclinical RNA-dependent RNA polymerase inhibitor that was efficacious in a mouse model of infection (NIAID)
- Supported preclinical studies on several CHIKV vaccine platforms, including two viral vectored vaccines, and a novel, live-attenuated infectious DNA vaccine platform (NIAID)
- Screened 492 candidate small molecules; 11 of which had moderate-to-high activity against CHIKV (NIAID)
- Demonstrated high activity against CHIKV in three of four antibodies screened in mouse models (NIAID)
- Developed a point-of-care diagnostic tool to distinguish between CHIKV and dengue virus (NIAID)

[11] https://www.cdc.gov/chikungunya/transmission/index.html

Clinical Research

- In 2018, concluded a virus-like particle vaccine candidate (CHIKV-VLP) Phase 2 multisite safety and efficacy vaccine clinical trial in endemic areas of the Caribbean (NCT02562482). PaxVax licensed the technology for this vaccine in 2017. (NIAID)
- In 2017, initiated a multisite Phase 1 dose-comparison clinical trial in the U.S. of a measles vaccine virus modified to produce CHIKV proteins (MV-CHIKV) (NCT03028441) (NIAID)

Dengue Fever

Dengue fever, a common mosquito-borne viral disease, occurs in most tropical and subtropical regions of the world.[12] Dengue fever is caused by four serotypes of dengue virus (DENV), a flavivirus transmitted to humans by *A. aegypti* and *A. albopictus* mosquitoes, which thrive in urban and semiurban environments. Most people infected with DENV experience no symptoms or only a mild fever. Others develop flu-like symptoms, headache, and joint and muscle pain. A subset experience more severe dengue hemorrhagic fever or shock syndrome, which can cause high fever, pain, bleeding, a sudden drop in blood pressure and, in some cases, shock syndrome and death.

Epidemiological Research

- Supported a 23-year natural history study in Thailand to identify factors related to disease severity in children (NIAID)
- Began investigating human gene variants that correlate with disease severity in a large international clinical study (NIAID)

Fundamental Research

- Supported the development of a tetravalent dose-sparing DENV1-4 subunit vaccine (NIAID)
- Conducted a bioinformatic meta-analysis to identify flavivirus-specific targets of immune responses, with a focus on DENV and ZIKV (NIAID)
- Determined that prior DENV exposure shapes immunity to Zika virus, including the timing, magnitude, and quality of the immune T cell response. These findings could impact future vaccine design. (NIAID)
- Discovered that prior dengue immunity in children may be protective against symptomatic Zika virus disease rather than be a risk factor, as previously thought. (NIAID)
- Determined that engineered DENV proteins elicit cross-neutralizing antibody responses in mice (NIAID)
- Investigated the role of programmed cell death regulation during the adaptive immune response to infection with different DENV strains, and its effects on viral replication (NIGMS)

[12] https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

- Used controlled models of human infection following vaccination to advance DENV vaccine development and improve understanding of DENV immune responses and key factors mediating protection (NIGMS)
- Supporting a compilation and analysis of large datasets to determine the spatial and timing dynamics of DENV transmission on a continental scale in Southeast Asia (NIGMS)

Translational Research

- Developed a VIS513 antibody that neutralizes all four serotypes of dengue. A partnership between Visterra and Serum Institute of India aims to conduct clinical trials with the goal of commercializing VIS513 in endemic countries (NIAID)

Clinical Research

- Evaluated an antiviral drug candidate (UV-4b) developed with Emergent Virology (with NIAID support) in a Phase 1 clinical trial for safety and pharmacokinetics (NCT02061358) (NIAID)
- Discovered a tetravalent dengue vaccine (TV003) that protected all recipients in a virus challenge study (NCT03416036) (NIAID)
- Takeda is testing a tetravalent, recombinant vaccine (DENVax) in Phase 3 trials in endemic countries. The vaccine was developed with partial NIAID support (NCT: 01511250; 02302066; 02948829; 02747927)
- Performed an interim analysis of a Phase 2 clinical trial that indicated reduced dengue incidence in youth (NIAID)
- Found that a live, attenuated tetravalent vaccine (TetraVax-DV) licensed to industry partners worldwide was 100 percent protective in a human challenge study. Several international clinical trials are ongoing (NCT02406729, NCT02678455, NCT03485144) (NIAID)

Lyme Disease and Other Tickborne Diseases

Ticks are capable of transmitting a variety of disease-causing pathogens, including those responsible for Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, babesiosis, and Powassan disease.[13] Lyme disease, the most prevalent of the tick-transmitted infections in the U.S., is caused by the bacterium *Borrelia burgdorferi*. It causes such symptoms as fever, headache, stiff neck, body aches, fatigue, and, in some individuals, a rash at the site of the tick bite that looks like a bull's eye. For reasons that are still unclear, a small percentage of patients report a range of sometimes debilitating symptoms, known as post-treatment Lyme disease syndrome, continuing years after standard antibiotic treatment. NIH supports an extensive and diverse research portfolio to advance understanding of Lyme disease and other TBDs and to better diagnose, prevent, and treat these conditions.

[13] https://www.cdc.gov/ticks/diseases/index.html

Epidemiological Research

- Estimated the health burden of a newly emerging pathogen, *B. miyamotoi*, in the northeast U.S. and California through prospective serosurveys and case finding studies (NIAID)
- Determined exposure frequencies of small mammals to relapsing fever bacteria in Panama and identified novel isolates/species of these bacteria in field-collected ticks and small mammals (NIAID)
- Analyzed data and found that in a group of children diagnosed with Lyme disease across six emergency departments, fewer than 20 percent had a recognized tick bite (NICHD)

Fundamental Research

- Updated the NIAID *Current Efforts in Lyme Disease Research 2017* report,[14] originally published in 2015. This report provides updates for FY 2016–2017 on basic, translational, and clinical research activities (NIAID)
- Identified the causal role of tick bites in galactose-alpha-1,3-galactose (alpha-gal) red-meat allergy, which induces anaphylactic reactions in response to red-meat consumption (NIAID)
- Developed an oral bait vaccine to prevent a natural wildlife reservoir (white-footed mouse) from becoming infected with Lyme disease-causing bacteria (NIAID)
- Discovered a new bacteria species, *B. mayonii,* that can cause Lyme disease (NIAID)
- Developed animal models to better understand the relapsing-fever pathogen, *B. miyamotoi*, spread by the same tick that transmits Lyme disease (NIAID)
- Explored how *B. burgdorferi* maintains its unique genomic structure and described the specific contributions of individual plasmids and genes at each stage of the pathogen's infectious cycle among ticks and mammals (NIAID)
- Examined the role of specific bacterial proteins in how *B. burgdorferi* infects and persists in the host (NIAID)
- Developed animal models to explore the impact of *Borrelia-Babesia* coinfection on the pathogenesis of these diseases (NIAID)
- Developed a new culture model to study ticks that transmit flaviviruses, including Powassan virus (NIAID)
- Characterized the function of proteins that may be important virulence factors in bacteria that cause Rocky Mountain spotted fever (NIAID)
- Showed that the infection history in the host from whom the tick feeds can have a profound impact on the virulence of the Lyme disease spirochete, even before the Lyme disease spirochete leaves the tick and enters the host (NIAID)
- Determined how the bacterial waste that remains after treatment of the causative agent of Lyme disease, *B. burgdorferi*, induces inflammatory responses that lead to neurological dysfunction (NIGMS)

[14] https://www.niaid.nih.gov/sites/default/files/NIAIDLymereport2017.pdf

- Identified the pathogenesis of tick-borne relapsing fever spirochetes and the virulence factors and regulators required by the bacteria during infection (NIGMS)

Translational Research

- Investigating whether existing Lyme disease canine vaccines can be adapted for use in humans (NIAID)
- Identified metabolic biosignatures in various clinical samples to detect early Lyme disease and to differentiate between Lyme disease and look-alike infections (NIAID)
- Developed a microfluidics-based, point-of-care, multiplex test for early diagnosis of Lyme disease (NIAID)
- Identified biomarkers, such as C-reactive protein, that are distinctly higher in patients with antibiotic-refractory Lyme arthritis and post-treatment Lyme disease syndrome (NIAID)
- Re-purposed existing antibiotics for the effective treatment of patients with post-treatment Lyme disease syndrome (NIAID)
- Investigating vaccine approaches targeting tick salivary proteins critical for the transmission of Lyme bacteria to humans (NIAID)
- Developing an early diagnostic test that can detect Lyme disease and multiple other tick-transmitted pathogens (NIGMS)

Clinical Research

- More than 500 patients participate in NIH Clinical Center studies, including patients with post-treatment Lyme disease syndrome. These studies involved the following:
    - Evaluating, treating, and conducting follow-up visits for Lyme disease patients to assess the clinical course, outcomes, and immune response to infection (NCT00028080) (NIAID)
    - Evaluating patients with post-treatment Lyme disease syndrome with the goal of developing stringent diagnostic criteria for Lyme disease (NCT00001539) (NIAID)
    - Evaluating xenodiagnosis, an approach that uses deer ticks to detect the presence of persistent bacteria in people after completion of antibiotic therapy, to test for the presence of *B. burgdorferi* infection (NCT02446626, NCT01143588) (NIAID)
    - A retrospective review study that suggested that an intra-articular glucocorticoid injection to be an effective and safe second-line treatment for persistent Lyme arthritis in children (NIAMS, NICHD)[15]

Malaria

Human malaria, caused by parasites (*Plasmodium falciparum* and others) and transmitted by *Anopheles* mosquitoes, remains the most significant parasitic disease globally in terms of annual mortality. Considerable progress has been made in the global fight to control and eliminate malaria through improved prevention and control efforts. Between 2000 and 2017, the worldwide rate of new malaria

[15] Horton DB, et al. *J Rheumatol* 2019;46(8):952-59. PMID: 30824649.

cases decreased by 18 percent, although no significant progress was made in reducing malaria cases since 2015, according to the WHO.[16] Despite the progress made to curb malaria's global impact, nearly half of the world's population remains at risk. NIH is leveraging its comprehensive research program to achieve the goal of eliminating malaria.

Epidemiological Research

- Began surveying a genetic marker of treatment failure throughout Southeast Asia to monitor the spread of piperaquine resistance and determine where alternative therapies should be used (NIAID)
- Worked with local scientists in Southeast Asia and Africa to define the response to the antimalarial drug artemisinin and inform malaria treatment approaches (NIAID)
- Evaluated the impact on malaria transmission of cross-border movement of people from endemic areas to non-endemic areas (NIAID)
- Studied the impact of public health control interventions on the molecular diversity of malaria parasites (NIAID)

Fundamental Research

- Identified the receptor(s) and signaling molecules involved in *P. falciparum* activation of beta-catenin, a critical molecule that regulates blood–brain barrier integrity, in cerebral malaria (NHLBI)
- Identified genetic markers associated with increased piperaquine resistance in Cambodia, providing additional genetic markers for drug-resistance surveillance (NIAID)
- Determined essential malaria parasite genes that may represent good targets for antimalarial compounds (NIAID)
- Characterized vaccine-induced immunity and identified correlates of protection to guide new vaccine design and development (NIAID)
- Identified a parasite-specific maternal antibody that may protect infants against malaria infection, suggesting that vaccination during pregnancy may afford a survival advantage to infants (NIAID)
- Created a comprehensive, publicly accessible *P. falciparum* database and generated guidelines for CRISPR-Cas9 alteration of this parasite (NIAID)
- Discovered that infected red blood cell vacuoles where malaria parasites change shape before they rupture and release malaria parasites into the bloodstream, and that this shape can be chemically blocked (NICHD)
- Determined that the deadliest malaria parasite needs two proteins, plasmepsin IX and plasmepsin X, to infect red blood cells and exit cells after multiplying. This finding offers potential for new drug development (NICHD)
- Advanced understanding of how plasma cells function during adaptive immune responses to malaria infection to improve the efficiency of vaccines (NIGMS)

[16] https://www.who.int/malaria/media/world-malaria-report-2018/en/

- Determined the mechanisms that malarial sporozoites found in mosquito salivary glands and the human liver use to invade cells, with the goal of identifying novel vaccine targets (NIGMS)
- Determined how dihydrofolate reductase (DHFR)-resistant phenotypes can be used to develop novel approaches to drug treatment that will prevent or delay evolution of malaria drug resistance (NIGMS)
- Studied gene expression of avian malaria parasites to understand their evolution of pathogenicity and to identify genes that cause morbidity (NIGMS)

Translational Research

- Assisted in showing that nitric oxide was protective against severe malaria and is increasing our understanding about the role that an important part of the vascular barrier, the endothelial glycocalyx, plays during malaria (NHLBI)
- Supported product development of four antimalarial drugs and seven malaria vaccine candidates currently in clinical trials (NIAID)
- Developing fully automated software—which will be integrated with low-cost, portable retinal cameras—to detect cerebral malaria in young children in resource-limited areas (NIAID)
- Developed a new mouse model of pregnancy malaria that mimics several important features of human pregnancy malaria (NIAID)
- Identified a human monoclonal antibody, CIS43, with potential therapeutic and vaccine design implications that prevents malaria infection by targeting a new site of vulnerability on the parasite (NIAID)
- Determined that extra iron supplementation interferes with the function of ferroportin, a protein that prevents toxic buildup of iron in red blood cells and helps protect these cells against malaria infection (NICHD)
- Characterized a novel blood-stage malarial vaccine candidate using animal models of infection and validated the generalizability of protective human immune responses in a cohort of Tanzanian children (NIGMS)

Clinical Research

- Began supporting a Phase 4 clinical trial comparing three chemoprevention regimens to prevent malaria in children with sickle cell anemia in Kenya (NCT03178643) (NHLBI)
- Completed the first-ever field trial of a whole-organism vaccine (Sanaria's PfSPZ vaccine) (NCT02015091) (NIAID)
- Conducting a Phase 1 clinical trial in Mali on a second-generation, nanoparticle-based malaria transmission-blocking vaccine; a Phase 2 trial is planned (NCT02942277) (NIAID)
- Began supporting a Phase 3 clinical trial in Malawi to assess whether hypertonic saline or early mechanical ventilation might reduce mortality in children presenting with cerebral malaria (NCT03300648) (NIAID)
- Conducted an observational clinical trial showing that pregnant women using prophylactic medication combined with indoor insecticide spraying and treated bed nets had significantly

lower rates of malaria during pregnancy, as well as improved birth outcomes (NCT02163447) (NICHD)

West Nile

West Nile virus (WNV) is a flavivirus that primarily cycles between mosquitoes and birds but can be transmitted to humans through the bite of an infected *Culex* mosquito.[17] WNV is well established in the U.S. and many countries in Europe and the Middle East. Most serious cases occur in people older than 50 years of age and in those with impaired immune systems. In a small number of cases, WNV has been spread via blood transfusions, organ transplants, and breastfeeding.

Fundamental Research

- Developed novel animal models that better recapitulate human WNV disease outcomes (NIAID)
- Discovered gene variants that confer susceptibility or resistance to WNV infection (NIAID)
- Supported the development of a dose-sparing bivalent WNV/ZIKV vaccine (NIAID)

Translational Research

- Developed a simple microfluidic device for point-of-care, antibody-based diagnosis of arboviruses, including WNV (NIAID)
- Developed two candidate broad-spectrum immunotherapeutics that target RNA viruses, including WNV (NIAID)
- Developed two promising vaccine candidates; a live, attenuated WNV vaccine and an investigational WNV DNA vaccine (NIAID)

Clinical Research

- Tested a hydrogen peroxide–inactivated WNV vaccine candidate developed by Oregon Health & Science University and Najit Technologies in a Phase 1 clinical trial. The vaccine was safe and tolerable, but weakly immunogenic (NCT02337868). A future clinical trial with a higher dose is planned. (NIAID)
- Showed the safety and immunogenicity of a chimeric live attenuated West Nile virus vaccine (rWN/DEN4Δ30) in flavivirus-naive adults aged 50–65 years old (NCT02186626) (NIAID)

Zika

Zika virus (ZIKV) is primarily transmitted to humans through the bite of infected *A. aegypti* mosquitoes.[18] ZIKV can be transmitted from an infected woman to her baby during pregnancy and can result in serious birth defects, including microcephaly. In May 2015, the Pan American Health Organization issued an alert regarding the first confirmed ZIKV infection in Brazil. Since that time, Brazil and other countries and

[17] https://www.cdc.gov/westnile/transmission/index.html
[18] https://www.cdc.gov/zika/about/index.html

territories in Central and South America, as well as the Caribbean (including Puerto Rico and the U.S. Virgin Islands) have experienced ongoing ZIKV transmission. NIH is working with its partners in government, academia, and the pharmaceutical and biotechnology industries to better understand ZIKV, the disease it causes, and ways to combat it.

Epidemiological Research

- Established a blood specimen collection from a natural history cohort infected with ZIKV that can be used to assess the kinetics of viremia and immune responses to ZIKV infection for different blood compartments (NHLBI)
- Began evaluating the presence of ZIKV, as well as DENV and CHIKV, in blood donors in Brazil (NHLBI)
- Began supporting natural history studies in Brazil and Nicaragua to look at ZIKV transmission in family clusters, viral shedding in different bodily fluids, and the role of preexisting immunity to dengue and ZIKV disease (NIAID)
- Began researching the persistence of Zika viral RNA in body fluids to learn about time frames of transmissibility and diagnostic detection in travelers returning to the U.S. (NIAID)
- Began investigating postnatally acquired ZIKV in rural Guatemala to characterize clinical manifestations, assess impact on neurodevelopment, and determine the virology (NIAID)

Fundamental Research

- Developed robust, high-throughput screening assays and screened more than 90,000 compounds to identify those with anti-ZIKV activity (NCATS)
- Demonstrated how ZIKV can infect and kill the neural progenitor cells that give rise to the cerebral cortex and identified compounds that can inhibit ZIKV infection and reduce the ability of ZIKV to kill brain cells (NCATS/NINDS)
- Discovered that two ZIKV proteins, NS4A and NS4B, work together to block the cell signals needed for normal brain development (NHLBI, NIAID, NIDCR)
- Showed that ZIKV can infect and replicate in primary human placental macrophages, suggesting a mechanism for intrauterine transmission (NIAID)
- Published a full-length infectious cDNA clone of ZIKV from the 2015 epidemic in Brazil as a genetic platform for studies of virus-host interactions and vaccine development (NIAID)
- Showed that cells from early pregnancy contain many traits enabling viral infection that are not present in trophoblasts later in pregnancy. Identified characteristics of trophoblasts in late pregnancy that appeared to help fight infections (NICHD)

Translational Research

- Identified a repurposed drug (emetine) with anti-ZIKV replication activity and demonstrated the in vivo antiviral efficacy of emetine in ZIKV infection mouse models (NCATS)

- Began assessing the minimum infectious dose that will lead to transfusion-transmission of ZIKV through blood products and the effectiveness of pathogen-reduction techniques in mitigating transfusion-transmission of ZIKV in a macaque model (NHLBI)
- Began developing a superfluid-based technology for inactivating blood-borne viruses and other pathogens, including ZIKV (NHLBI)
- Generated an antibody, ZIKV-117, that provides protection in mice with active ZIKV infection and may reduce mother-to-fetus transmission and neutralize ZIKV that reaches the fetus (NIAID)
- Generated two novel recombinant vesicular stomatitis virus (VSV)-ZIKV vaccines using the favorable immune targeting of the existing VSV-Ebola virus vector (NIAID)
- Developed a mouse model of ZIKV vertical transmission (NIAID)
- Developed two mouse models of ZIKV infection in pregnancy that show how ZIKV damages the placenta and fetuses (NIAID, NICHD)
- Found that ZIKV induces high levels of inflammation in the blood vessels that transfer oxygen and nutrients from maternal blood to the fetus in a monkey model, which can lead to stillbirth and other adverse outcomes (NICHD)
- Found that approximately 26 percent of ZIKV-infected pregnant primates experienced miscarriages or fetal deaths, compared with 4 to 11 percent of uninfected animals (NICHD)
- Showed that ZIKV infection was associated with damaged testicular tissue, lower testosterone and other hormone levels, and reduced sperm counts (NICHD)
- Developing rapid, noninvasive, point-of-care salivary diagnostics to improve detection of ZIKV infections in pregnant women and other vulnerable individuals (NIDCR)

Clinical Research

- Conducted a Phase 1 clinical trial in collaboration with Walter Reed Army Institute of Research (WRAIR), Biomedical Advanced Research and Development Authority (BARDA), and Sanofi Pasteur to test a whole-particle-inactivated ZIKV vaccine that was well tolerated and induced an immune response in recipients (NCT03008122, NCT02963909, NCT02952833, NCT02937233) (NIAID)
- Demonstrated the DNA vaccine candidate VRC 705 to be well tolerated in a multisite Phase 2/2b safety and efficacy clinical trial conducted in areas of confirmed or potentially active ZIKV infection (NIAID)
- Began conducting a Phase 1 first-in-human trial of a live, attenuated ZIKV vaccine on a DENV vaccine backbone; a combination ZIKV/DENV vaccine is now in development (NCT03611946) (NIAID)

Other Vector-Borne Diseases

Fundamental Research

- Determined 3-D structures of proteins important to the pathogens that cause Chagas disease, leishmaniasis, river blindness, and other vector-borne diseases (NIAID)

- Demonstrated that ingestion of a second uninfected blood meal by Leishmania-infected sand flies triggers dedifferentiation of the parasite, whereas feeding on infected hosts amplified parasites 125-fold (NIAID)
- Showed in tests on human placenta cells that Rift Valley fever virus has a unique ability to infect a specialized layer of cells that supports the region of the placenta where nutrients flow (NICHD)
- Characterized the biochemical, structural, and functional mechanisms by which CRISPR-Cas complexes of *Francisella tularensis novicida* enhance the pathogenicity of the bacteria by reducing the expression of a bacterial lipoprotein essential for host recognition and immune response (NIGMS)
- Identified the mechanisms by which *Yersinia pestis* evades macrophage detection and killing and defined the contribution of intracellular survival to *Y. pestis* virulence (NIGMS)
- Studied the structure and function of SLC7-type cationic amino acid transporters of the yellow fever mosquito, *A. aegypti*, to understand nutrient signaling pathways and their role in regulating mosquito reproduction (NIGMS)

Translational Research

- Began developing highly specific and sensitive assays for early-stage detection of rickettsia, ehrlichia, and orientia infection to enable timely treatment and assessment of treatment (NCATS)
- Identified the antimalarial drug pyronaridine as a potential treatment for Chagas disease using computational Bayesian repurposing methods (NCATS)
- Used LoaScope, a custom smartphone-based video microscope, to rapidly test 16,259 people in an antiparasitic treatment effort previously halted after the occurrence of fatal events related to Loa loa infection. LoaScope use could revolutionize antiparasitic efforts in Africa (NIAID)
- Developed a recombinant, protein-based vaccine for schistosomiasis and hookworm (NIAID)
- Began developing a serodiagnostic test for Chagas disease (NIAID)

Clinical Research

- Began evaluating the safety and efficacy of a recombinant smallpox-based vaccine candidate for yellow fever (MVA-BN-YF) in a Phase 1 clinical trial. The vaccine was developed to address availability and reactogenicity issues in the current vaccine, (NCT02743455) (NIAID)
- Began a Phase 1 clinical trial in collaboration with industry partners to test a universal mosquito saliva vaccine (AGS-V) that is designed to trigger a protective immune response to mosquito saliva to prevent transmission of mosquito-borne infections (NCT03055000) (NIAID)

Vector Control Strategies

NIH conducts and supports a comprehensive vector biology research program to advance science and identify approaches that will help control or prevent the transmission of vector-borne pathogens to humans. This program includes a variety of basic, translational, and clinical research projects that will contribute to a better understanding of key aspects of the biology of arthropod vectors. The translational

program supports the development of products to reduce vector populations or to prevent vectors from coming into contact with people. The clinical projects evaluate products and approaches designed to prevent the transmission of pathogens to humans.

Fundamental Research

- Began researching insecticidal molecules as a means of mosquito control (NIAID)
- Began conducting studies on dengue vector competence and *Aedes* species insecticide resistance in Brazil (NIAID)
- Developed a smartphone-based citizen science surveillance technology to identify the presence and distribution of mosquitoes that can transmit DENV and other vector-borne diseases (NIAID)
- Supported sequencing efforts to update and improve the known mosquito genome for *A. aegypti*, a mosquito species that can transmit such viruses as dengue, yellow fever, and Zika (NIAID, NIDCD)
- Began supporting research on the molecular basis of the spatial repellency of pyrethroids—insecticides used to control insect vectors that transmit human disease. Spatial repellency protects people from vector-borne diseases by reducing contact between people and vectors, thereby reducing disease transmission (NIGMS)
- Began funding research to develop a Mutagenic Chain Reaction method, a CRISPR/Cas9-based technique to drive transgenes through a population, which is ultimately intended to be used to knock down/out disease vectors in insect carriers (NIGMS)
- Began developing decision support tools and dynamic decision models for disease intervention and surveillance strategies (NIGMS)
- Began working on the effects of temperature on mosquito life history and vector competence (NIGMS)
- Began modeling the control of environmentally transmitted pathogens (NIGMS)

Translational Research

- Began investigating the use of larvicide-treated male mosquitoes and *Wolbachia* bacterial infection of mosquitos for mosquito population control (NIAID)
- Improved the Autocidal Gravid Ovitrap as an intervention for *Aedes* mosquito control. This intervention will be commercialized with the goal of reducing *Aedes* mosquito populations in urban and rural areas (NIAID)
- Used gene editing to modify the genome of *A. stephensi* mosquitoes to block malaria transmission (NIAID)

Clinical Research

- Supported a clinical trial to assess the impact of the antiparasitic drug ivermectin as a repurposed therapy to control the mosquito vector of malaria (NCT02511353) (NIAID)
- Began supporting a clinical trial to assess the impact of *Wolbachia*-infected mosquitoes in reducing the transmission of DENV in Brazil (NCT03055585) (NIAID)

Committees

- ***The Federal Vector-borne Disease Integrated Pest Management Working Group*** permits agency representatives to discuss updates and important developments regarding vector-borne diseases, particularly vector control. (NIAID)
- ***The HHS Tickborne Disease Working Group*** was established by Congress in 2016 as part of the *21st Century Cures Act* to provide subject-matter expertise and to review federal efforts related to all tick-borne diseases, to help ensure interagency coordination and minimize overlap, and to examine research priorities. Representatives from NIAID participate in this committee. The first working group report to Congress was submitted to Congress in November 2018. (NIAID)
- ***The Tularemia Animal Model Qualification Working Group*** collaborates on the qualifications of primate models of pneumonic tularemia under the FDA Animal Model Qualification/Drug Development Tools Program. The collaboration includes the exchange of study data, study reports, and agreements on a regulatory strategy for model qualification. (NIAID)
- ***The U.S. Government Zika Vaccine Development Interagency Working Group*** was established by HHS and includes representatives from various U.S. government agencies (BARDA, CDC, DoD, FDA, NIH, WRAIR) to coordinate research efforts, mobilize domestic and international research infrastructure, and form partnerships with industry to accelerate the development of a safe and effective ZIKV vaccine. (NIAID)

Programs

- ***The International Centers of Excellence for Malaria Research (ICEMR)*** is a global network established to better understand malaria in endemic settings and strengthen local research capacity. The ICEMR program partners with the Bill & Melinda Gates Foundation to address important malaria-related research questions. In 2016, the ICEMR played a key role in sequencing the complete genomes of 200 strains of *P. vivax*, one of the five parasite species that cause malaria in humans. (NIAID)
- ***The NIAID Vector Biology Program*** conducts and supports a comprehensive vector biology research program to advance science and identify and test approaches that will help control or prevent the transmission of vector-borne pathogens to humans. This research includes the development of traps and repellents, the testing of such biologicals as *Wolbachia* bacteria, and the evaluation of novel candidate vaccines based on mosquito saliva. (NIAID)
- ***The Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)*** is a blood safety research program designed to ensure safe and effective blood banking and transfusion medicine practices. Five research studies are underway in the U.S. and Brazil to evaluate the presence of ZIKV, DENV, and CHIKV in blood donors and recipients. These studies are also evaluating the relationship between viral burden and the frequency of transfusion-transmitted infection. The results will inform worldwide blood screening policies and strategies for preventing transmission of these viruses via blood transfusion. (NHLBI)
- ***Therapeutics for Rare and Neglected Diseases (TRND)*** program encourages and speeds the development of new treatments for diseases with high unmet medical needs. This includes

vector-borne tropical diseases, such as schistosomiasis and malaria. TRND stimulates therapeutic development research collaborations among NIH and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies working on rare and neglected illnesses. (NCATS)

- ***The Tropical Medicine Research Centers*** support a variety of efforts focused on neglected vector-borne diseases. These centers facilitate research on the cause, diagnosis, prevention, and treatment of neglected tropical diseases and work toward the creation of sustainable in-country research capacity. (NIAID)
- ***Zika in Infants and Pregnancy (ZIP)*** is a multicountry study to evaluate the magnitude of health risks that ZIKV poses to pregnant women and their developing fetuses and infants. (NIAID, NICHD, NIEHS)

Workshops

- ***Alpha-Gal Allergy Workshop*** explored causes and treatment options for the unusual and only recently recognized phenomenon of life-threatening allergic reactions to certain foods (such as mammalian, or red meat) and medicines that contain a specific sugar (alpha-gal), initiated by the bite of a Lone Star tick. (NIAID)
- ***Bridging Knowledge Gaps to Understand How Zika Virus Exposure and Infection Affect Child Development*** brought together researchers to identify optimal approaches for treating and caring for children exposed to ZIKV in the womb, whose care will take a multidisciplinary approach and require long-term monitoring. (NIAID, NICHD)
- ***Malaria: From Innovation to Eradication Keystone Symposia*** provided a forum for researchers to highlight progress toward the elimination and eradication of malaria, including fundamental research breakthroughs, development of next-generation tools, and other strategies to eliminate malaria. (NIAID)
- ***Mexico–U.S. Forum on Arboviral Diseases: Priorities for Research and Collaboration*** brought together investigators from Mexico and the U.S. interested in arboviral disease research (specifically ZIKV, DENV, and CHIKV) to identify areas of common interest. (NIAID)
- ***Middle East Regional Workshop on Endemic and Emerging Animal and Vector-Borne Diseases in the Levant: Potential Threats to Human Health and Agriculture (2016)*** focused on stimulating new or expanded scientific exchange, research training, and collaborative research projects among scientists from the Levant and U.S. (NIAID, NCATS)
- ***Rickettsiales: Host-Vector-Pathogen Interactions Workshop*** at the *28th Meeting of the American Society for Rickettsiology* provided a forum for scientific exchange among investigators who study rickettsial and other vector-borne diseases. The workshop focused on the latest, cutting-edge research on rickettsial and other diseases caused by arthropod-borne and obligate intracellular pathogens. (NIAID)
- ***Skin Immune Responses to Vector Bites Workshop*** examined how the bite from a blood-feeding arthropod affects the local immune environment at the bite site and subsequent transmission of vector-borne pathogens. Experts from vector biology, skin immunology, and infectious disease

research interacted to provide insights into what occurs at the site of a bite from an immunological and disease transmission perspective, including how local immune responses in the skin are altered by immunomodulatory molecules in the saliva of blood-feeding arthropods. (NIAID)

- ***The Arthropod Vector: The Controller of Transmission Keystone Symposia*** focused on the arthropod vector factors that influence the transmission of pathogens to humans. Topics included innate immunity, microbiome, saliva, and approaches to disease control. (NIAID)
- **Understanding Vaccine-Elicited Immunity to Malaria in Endemic Regions** focused on understanding the underlying protective immune mechanisms and other variables that impact malaria vaccine efficacy in the field and how advances in systems vaccinology and data sciences can help vaccinology and immunology research and guide future vaccine development efforts. (NIAID)
- ***Vectors, Pathogens and Diseases: Current Trends and Emerging Challenges Keystone Symposia*** highlighted fundamental, translational, and clinical research advances toward eliminating or controlling vector-borne diseases. The meeting also served as a platform for the cross-disciplinary and cross-insect exchange of ideas to enhance different areas of vector-borne disease research. (NIAID)
- ***Zika Virus Therapeutics Workshop*** covered the latest information on ZIKV by experts from federal agencies, academia, and pharmaceutical and biotechnology companies. Topics addressed at the workshop included virology, epidemiology, possible links between ZIKV and microcephaly, and efforts to develop diagnostics, therapeutics, and vaccines. (NIAID)
- ***Ethical Consultation for Zika Virus Human Challenge Trial*** was convened by NIAID and WRAIR to bring together scientists, ethicists, members of research review boards, and subject-matter experts from federal agencies to determine how best to address the ethical issues raised by a possible Zika virus human challenge study. An external committee developed recommendations on the potential conduct of Zika virus human challenge trials based on the data from scientific and clinical studies available as of December 2016. (NIAID)
- ***Immune Correlates and Surrogates for Zika Vaccine Development*** was convened by NIAID and WHO to identify strategies to demonstrate vaccine effectiveness in view of waning Zika disease incidence. Subject-matter experts from academic, industry, and regulatory agencies in the U.S. and around the world participated in the meeting to develop points for consideration for developers, regulators, and other stakeholders working toward a licensed Zika virus vaccine. (NIAID)

Appendix D:
Report of Trans-NIH Research

This report provides the dollar amounts made available by each NIH IC for conducting or supporting research that involves collaboration between that IC and one or more other ICs.

NIH is composed of 27 ICs, each having a distinct mission. Leaders across NIH recognize that scientific progress often comes at the interface of traditional boundaries. As a result, considerable collaborative activity occurs across IC boundaries at every level of NIH operations. Trans-NIH collaborative activities can be found in all disease areas and throughout basic, translational, and clinical research. These collaborations can be formal or informal and can involve sharing materials, specimens, or scientific expertise. Collaborations take place at any or all stages of a research project or program, including development of a concept, initiative, or plan; funding; conduct of the research in intramural laboratories; management and administration of the project; and assessment of results.

Trans-NIH research collaborations represent unique opportunities to build on the scientific expertise, sophisticated technologies, infrastructure, and knowledge base of individual ICs and to apply this wealth of information and resources to addressing a wide range of diseases and health conditions. These collaborations produce multidisciplinary and multifaceted approaches to critical scientific questions and lead to special initiatives and innovative programs for the discovery, development, and testing of strategies to diagnose, prevent, and treat a wide range of health conditions. Inter-IC collaborations also enable the leveraging of crucial resources to ensure precious research dollars are used effectively and efficiently to improve the public health of all Americans.

For the full information about FY 2016 and FY 2017–2018 trans-NIH collaborations, see the NIH Collaborations report: https://dpcpsi.nih.gov/oepr/nih-collaborations-report.

Appendix E:
Research Training and Graduate Medical Education Data

National Research Service Award (NRSA) and National Library of Medicine (NLM) Research Training Programs: Number of Ph.D. Recipients by Field of Study[1]

Field of Study Major and Minor Category	Description	FY of Ph.D. 2016	2017
Life sciences	**Overall**	**2,554**	**2,550**
Agricultural sciences and natural	**Subtotal**	**3**	**10**
	Animal Nutrition	0	0
	Animal Science, Other	0	2
	Environmental Science	1	3
	Food Science	2	2
	Natural Resources/Environmental	0	0
	Plant Pathology/Phytopathology	0	2
	Plant Sciences, Other	0	1
Biological and biomedical sciences	**Subtotal**	**2,336**	**2,320**
	Anatomy	1	1
	Bacteriology	4	3
	Biochemistry	194	201
	Bioinformatics	23	21
	Biomedical Sciences	70	83
	Biometrics & Biostatistics	32	46
	Biophysics	54	49
	Biotechnology	3	1
	Botany/Plant Biology	5	4
	Cancer Biology	148	123
	Cell/Cellular Biology & Histology	70	68
	Computational Biology	29	38
	Developmental Biology/Embryology	49	55
	Ecology	8	5
	Endocrinology	1	2
	Entomology	1	2
	Environmental Toxicology	4	10
	Epidemiology	72	93
	Evolutionary Biology	16	19

[1] Data were drawn from the Information for Management Planning Analysis and Coordination (IMPAC) II Current Files and Doctorate Records File on July 9, 2019, and are subject to change. CTSA trainees are included in the NRSA data provided.

Field of Study Major and Minor Category	Description	FY of Ph.D. 2016	 2017
	Genetics/Genomics, Human & Animal	126	140
	Immunology	178	173
Biological and biomedical sciences (cont'd)			
	Microbiology	133	130
	Molecular Biology	163	195
	Molecular Medicine	9	29
	Neurosciences & Neurobiology	439	427
	Nutrition Sciences	17	22
	Parasitology	3	5
	Pathology, Human & Animal	18	31
	Pharmacology, Human & Animal	75	71
	Physiology, Human & Animal	35	42
	Plant Genetics	9	2
	Plant Pathology/Phytopathology	1	1
	Structural Biology	14	17
	Toxicology	24	25
	Virology	60	45
	Wildlife Biology	0	0
	Zoology	0	0
	Biology & Biomedical Sciences, General	208	119
	Biology & Biomedical Sciences, Other	40	22
Health sciences	**Subtotal**	**215**	**220**
	Environmental Health	16	18
	Gerontology	5	1
	Health & Behavior	12	7
	Health Services Research	4	17
	Health Systems/Services Administration	1	1
	Kinesiology/Exercise Physiology	5	5
	Medical Physics/Radiological Science	12	12
	Nursing Science	54	55
	Oral Biology/Oral Pathology	7	6
	Pharmaceutical Sciences	18	24
	Public Health	39	38
	Rehabilitation/Therapeutic Services	7	7
	Speech-Language Pathology & Audiology	19	12
	Veterinary Sciences	6	5
	Health Sciences, General	6	4
	Health Sciences, Other	4	8
Physical sciences and earth sciences	**Overall**	**116**	**138**
Chemistry	**Subtotal**	**87**	**107**
	Analytical Chemistry	11	8
	Chemical Biology	20	39
	Inorganic Chemistry	7	3
	Medicinal Chemistry	5	9
	Organic Chemistry	19	17
	Physical Chemistry	7	6
	Polymer Chemistry	2	0
	Theoretical Chemistry	0	2

Field of Study Major and Minor Category	Description	FY of Ph.D. 2016	 2017
	Chemistry, General	8	20
	Chemistry, Other	8	3
Geosciences/atmospheric/ocean sciences	**Subtotal**	**4**	**4**
	Atmospheric Sciences/Meteorology, General	1	0
	Geological & Earth Sciences, General	1	0
	Marine Biology & Biological Oceanography	2	3
	Paleontology	0	1
Physics and astronomy	**Subtotal**	**25**	**27**
	Applied Physics	1	2
	Astrophysics	3	0
	Atomic/Molecular/Chemical Physics	1	0
	Biophysics	12	16
	Condensed Matter/Low Temperature Physics	1	0
	Particle (Elementary) Physics	0	2
	Photonics/ Optics	3	6
	Polymer Physics	1	0
	Physics, General	1	1
	Physics, Other	2	0
Mathematics and computer sciences	**Overall**	**26**	**25**
Computer and information sciences	**Subtotal**	**8**	**9**
	Computer Science	6	6
	Information Science & Systems	0	1
	Computer & Information Sciences, General	0	0
	Computer & Information Sciences, Other	2	2
Mathematics and statistics	**Subtotal**	**18**	**16**
	Applied Mathematics	5	4
	Geometry/Geometric Analysis	1	1
	Statistics	5	9
	Mathematics & Statistics, General	5	1
	Mathematics & Statistics, Other	2	1
Psychology and social sciences	**Overall**	**247**	**225**
Psychology	**Subtotal**	**176**	**170**
	Behavioral Analysis	1	0
	Clinical Psychology	73	61
	Cognitive Neuroscience	30	25
	Cognitive Psychology & Psycholinguistics	12	8
	Counseling	4	3
	Developmental & Child Psychology	10	13
	Educational Psychology	1	0
	Experimental Psychology	6	2
	Health & Medical Psychology	4	7
	Human Development & Family Studies	7	4
	Industrial & Organizational Psychology	1	0
	Neuropsychology/Physiological Psychology	5	9
	Personality Psychology	1	3
	Psychometrics & Quantitative Psychology	2	3
	School Psychology	0	14

Field of Study Major and Minor Category	Description	FY of Ph.D. 2016	 2017
	Social Psychology	6	9
	Psychology, General	10	4
Psychology (cont'd)			
	Psychology, Other	3	5
Social sciences	**Subtotal**	71	55
	Anthropology, Cultural	5	3
	Anthropology, General	1	0
	Economics	14	19
	Political Science & Government	2	1
	Sociology	23	17
	Area/Ethnic/Cultural Studies	2	0
	Criminal Justice & Corrections	1	0
	Demography/Population Studies	11	5
	Geography	0	0
	Gerontology	0	0
	Health Policy Analysis	3	5
	Linguistics	2	2
	Public Policy Analysis	2	3
	Statistics	0	0
	Social Sciences, General	2	0
	Social Sciences, Other	3	0
Engineering	**Overall**	**240**	**210**
	Aerospace, Aeronautical, & Astronautical Engineering	1	1
	Bioengineering & Biomedical Engineering	204	170
	Chemical Engineering	20	22
	Civil Engineering	0	0
	Electrical, Electronics, & Communications Engineering	1	9
	Industrial & Manufacturing Engineering	1	0
	Materials Science Engineering	6	1
	Mechanical Engineering	3	1
Other engineering	**Subtotal**	**4**	**6**
	Computer Engineering	2	1
	Engineering Mechanics	0	0
	Engineering Science	0	1
	Environmental/Environmental Health Engineering	1	1
	Operations Research	0	1
	Polymer & Plastics Engineering	0	1
	Engineering, Other	1	1
Other Fields	**Overall**	**18**	**26**
NIH Total	**Grand Total**	**3,201**	**3,174**

Demographic Characteristics of NRSA Participants[2]

Demographic Characteristic	FY 2016	FY 2017
Gender		
Female	**53.1%**	**53.1%**
Male	**44.0%**	**43.7%**
Unknown	**2.9%**	**3.2%**
Withheld	**0.0%**	**0.0%**
Race		
White	**64.1%**	**63.2%**
Asian	**15.4%**	**16.0%**
Black or African American	**7.2%**	**7.2%**
American Indian or Alaska Native	**0.6%**	**0.6%**
Native Hawaiian or Other Pacific Islander	**0.2%**	**0.2%**
Person Reporting More Than One Race	**4.6%**	**4.6%**
Withheld	**7.9%**	**8.3%**
Unknown	**0.1%**	**0.1%**
Ethnicity		
Hispanic or Latino	**11.7%**	**12.6%**
Not Hispanic or Latino	**83.5%**	**82.6%**
Unknown	**0.1%**	**0.1%**
Withheld	**4.7%**	**4.8%**

[2] The NRSA training grants are T32, T34, T35, T90, TL1, TU2, TL4 (with reporting of the latter starting in FY 2016). The fellowship grants are F30, F31, F32, and F33. Data were drawn from IMPAC II current files and the Doctorate Records File on July 8, 2019, and are subject to change. Race and ethnicity are self-reported. CTSA trainees are included in the NRSA data provided.

Successfully Completed Residency and Subspecialty Training by Academic Year

NIH Clinical Center Program Specialty	Completed		
	2015/2016	2016/2017	2017/2018
Allergy and Immunology	4	3	3
Blood Banking/Transfusion Medicine	3	2	2
Critical Care Medicine	3	3	4
Cytopathology	1	1	1
Endocrinology, Diabetes, and Metabolism	5	2	7
Hematology (Pathology)	2	2	2
Hematology-Oncology[3]	9	13	13
Hospice and Palliative Medicine	2	2	2
Infectious Disease	4	2	5
Medical Biochemical Genetics	3	1	2
Medical Genetics	2	4	3
Neurological Surgery[4]	0	1	1
Oncology[5]	4		
Pathology (Anatomic and Clinical)	3	3	4
Pediatric Endocrinology	1	2	2
Psychiatry	2	2	1
Reproductive Endocrinology[6]	0	0	3
Rheumatology	3	3	2
Vascular Neurology	4	2	3
Total	**55**	**48**	**60**

[3] The combined Hematology-Oncology training program launched in 2015–16 and was formed by combining the Hematology and the Oncology programs.
[4] The Neurological Surgery training program launched in 2016–17.
[5] The Oncology training program fully transitioned to the Hematology-Oncology training program the 2016–17.
[6] The Reproductive Endocrinology training program launched in 2017–18.

Appendix F:
Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

NIH has examined and reported aggregate inclusion enrollment information for its portfolio of NIH-funded clinical research since FY 1994. These reports are one component of the NIH policy on the Inclusion of Women and Minorities as Subjects in Clinical Research.

For each NIH IC that supports clinical research, triennial reports on inclusion have been produced with all NIH enrollment information for FY 2016–2018.

An NIH-wide report covering FY 2015–2016, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, is published as Section IV (starting on page 37) of the *Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2015–2016.* Similarly, an NIH-wide report covering FY 2017–2018, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research,* is published as Section IV (starting on page 38) of the *Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2017–2018.*

For links to the NIH-wide biennial reports, as well as each IC's triennial report, please see https://report.nih.gov/research/inclusion-women-and-minorities-clinical-research#/.

Appendix G:
Catalog of Disease Registries, Databases, and Biomedical Information Systems

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
3-D Swarms	NIAID	NIAID	NIAID
4D Nucleome Data Coordination and Integration Center	NCI	OD/OSC (Common Fund)	Harvard University
4D Nucleome Web Portal	NCI	OD/OSC (Common Fund)	University of California, San Diego
A Bayesian Nonparametric Collaborative Filtering Algorithm to Improve Health Care Decisions	NLM	NLM	Medical University of South Carolina
A General Framework to Account for Outcome Reporting Bias in Systematic Reviews	NLM	NLM	University of Pennsylvania
A Knowledge-Based Message Tailoring System	NLM	NLM	University of Michigan at Ann Arbor
A Microaggregation Framework for Reproducible Research with Observational Data: Addressing Biases While Protecting Personal Identities	NLM	NLM	The University of New Mexico Health Sciences Center
A New Generation Clinical Decision Support System	NLM	NLM	University of Pittsburgh at Pittsburgh
A Novel Graph Processing Architecture to Ascertain & Monitor Care Coordination	NLM	NLM	Northwestern University
A Novel Informatics Approach to Understanding Complex Muscle Fiber Phenotypes	NLM	NLM	Brigham and Women's Hospital
A Research Opportunity Index to Measure Biomedical Research	NLM	NLM	Mayo Clinic Rochester

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Disparities Across the Disease Landscape			
A Search Engine for Heterogeneous Information Needs in the Clinical Workflow	NLM	NLM	Medsocket of Missouri, Inc.
Accelerating Biomedical Image Processing Using Massively Parallel Processors	NLM	NLM	Accelereyes, LLC
Accelerating Medicines Partnership (AMP) Type 2 Diabetes Knowledge Portal	NIDDK	NIDDK	Broad Institute, Inc.
AccessGUDID Tool to Search Global Unique Device Identification Database	NLM, FDA	NLM	NLM, FDA
Action for Health in Diabetes (Look AHEAD) and Follow-Up Study	NIDDK	NIDDK, NHLBI, ORWH	Multiple (Wake Forest School of Medicine, DCC)
Acute Liver Failure Registry in the Adult Acute Liver Failure Study Group (ALFSG)	NIDDK	NIDDK	Multiple (The University of Texas Southwestern Medical Center, DCC)
ADD: Pattern Analysis of fMRI via Machine Learning/Sparse Models: Application to Brain Development	NIBIB	NIBIB	University of Pennsylvania
Advancing CBPR Practice Through a Collective Reflection and Measurement Toolkit	NINR	NINR	The University of New Mexico Health Sciences Center
Advancing Methods to Measure and Improve the Quality of Large-Scale Health Data	NLM	NLM	Indiana University–Purdue University at Indianapolis
African American Cardiovascular Pharmacogenomics Consortium (ACCOuNT)	NIMHD	NIMHD	Northwestern University
AIDSinfo / infoSIDA	NLM	NLM, NIAID, OD/OAR	NLM ICF, Inc., LLC
Alcohol Policy Information System (APIS)	NIAAA	NIAAA	CDM Group, Inc.
ALTBIB: Resources for Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Alu Pairs Database	NIEHS	NIEHS, NLM	Genetic Information Research Institute
Alzheimer's Disease Neuroimaging Initiative (ADNI)	NIA	NIA, NIMH, NINDS, NINR	University of California, San Francisco
Alzheimer's Disease Patient Registry (ADPR)	NIA	NIA	Group Health Cooperative
Alzheimer's Disease Patient Registry (ADPR)	NIA	NIA	Mayo Clinic College of Medicine, Rochester
AMD Systems Biology	NEI	NEI	NEI
American Indian Health	NLM	NLM	NLM
An Integrative Bioinformatics Platform with Application in Single Cancer Cells	NLM	NLM	University of Hawaii at Manoa
Anti-Glycan Reagents	NCI	NCI	
AphasiaBank: A Shared Database for the Study of Aphasic Communication	NIDCD	NIDCD	Carnegie-Mellon University
AptaTRACE	NLM	NLM	NLM
Asia-Pacific HIV Research Collaboration (IeDEA)	NIAID	NIAID, NCI, NICHD, NIMH, NIDA	Foundation for AIDS Research
Asthma Birth Cohorts Database	NIAID	NIAID	NIAID
Atlas of Mouse Liver Lesions	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
Audiological and Genetic Resource for Pediatric Hearing Research	NIDCD	NIDCD	Children's Hospital of Philadelphia
Autism Genetic Resource Exchange (AGRE)	NIMH	NIMH, NICHD	Autism Speaks, Inc.
Automated Real-Time Trauma Resuscitation Communication System for Clinical Decision Support	NLM	NLM	Lifeboard Medical
AVIPORT: A Resource for Avian Biology	NICHD	NICHD	The University of Arizona
BETRNet Patient Registry-Virtual Biorepository	NCI	NCI	Vanderbilt University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
BeWith Software Tool	NLM	NLM	NLM
Bioconductor: An Open Computing Resource for Genomics	NHGRI	NHGRI	Roswell Park Cancer Institute Corporation
BioGRID: An Open Integrated Resource for Biological Interaction Data	OD/ORIP	OD/ORIP	Mount Sinai Hospital Lunenfeld-Tanenbaum Research Institute
Biological Specimen and Data Repositories Information Coordinating Center (BioLINCC)	NHLBI	NHLBI	Information Management Services, Inc.
Biomedical Informatics Research Network (BIRN) Data Repository	NINDS	NINDS	University of California, San Diego
Biomedical Translational Research Information System (BTRIS)	CC	CC	NIH Clinical Center
Biomedical Translator	NCATS	NCATS	NCATS
BioPlex: Systematic Exploration of the Human Interactome	NHGRI	NHGRI	Harvard Medical School
Biospecimen Exchange for Neurological Disorders or Diseases (BioSEND) Biomarkers Repository	NINDS	NINDS	Indiana University
Biospecimen Research Database	NCI	NCI	NCI
Biosystems Database	NLM	NLM	NLM
BLAST: Basic Local Alignment Search Tool	NLM	NLM	NLM
Block and Object Storage Service Database (bossDB)	NIMH	NINDS	Johns Hopkins University
Blueprint Neurotherapeutics Database	NINDS	NINDS	Collaborative Drug Discovery, Inc.
Bookshelf	NLM	NLM	NLM
Breast and Colon Cancer Family Registries	NCI	NCI	Multiple
Breast Cancer Information Core (BIC)	NHGRI	NHGRI	NHGRI
Breast Cancer Surveillance Consortium	NCI	NCI	Multiple

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
CADD Group Chemo Informatics Tools and User Services	NCI	NCI	NCI
Cancer Control P.L.A.N.E.T.	NCI	NCI	NCI
Cancer Data Access System (CDAS) for Prostate, Lung, Colorectal and Ovarian Cancer (PLCO): National Lung Screening Trial; and Interactive Diet and Activity Tracking in AARP studies	NCI	NCI	NCI
Cancer Epidemiology Descriptive Cohort Database (CEDCD)	NCI	NCI	NCI
Cancer Intervention and Surveillance Modeling Network (CISNET)	NCI	NCI	NCI
Cancer Nanotechnology Laboratory (caNanoLab)	NCI	NCI	NCI
Cancer Prevalence and Cost of Care Projections	NCI	NCI	NCI
Cancer Research Network	NCI	NCI	NCI
Cancer Survivor Prevalence Data	NCI	NCI	NCI
Cancer Systems Biology Consortium (CSBC)/Physical Sciences in Oncology Network (PS-ON) Knowledge Portal	NCI	NCI	Sage Bionetworks
Cancer Therapy Evaluation Program Enterprise (CTEP-ESYS)	NCI	NCI	NCI
Cancer Trends Progress Report	NCI	NCI	NCI
CAPE	NLM	NLM	NLM
Cardiovascular Research Grid (CVRG)	NHLBI	NHLBI	Johns Hopkins University
CCASAnet: Caribbean, Central and South America Network	NIAID	NIAID, NCI, NICHD, NIMH, NIDA	Vanderbilt University School of Medicine
Cell Image Library	NIGMS	NIGMS	University of California, San Diego
CellMiner	NCI	NCI	NCI

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Center for International Blood and Marrow Transplant Research (CIBMTR)	NCI	NCI, NHLBI, NIAID	Medical College of Wisconsin and the National Marrow Donor Program
Center for Molecular Microscopy	NCI	NCI	NCI
Center for Research in Reproduction Ligand Assay and Analysis Core	NICHD	NICHD	University of Virginia
Center for Strategic Scientific Initiatives (CSSI) Data Coordinating Center	NCI	NCI	NCI
Center for Viral Systems Biology	NIAID	NIAID	Scripps Research Institute
Center for Zebrafish Chromatin and Epigenetics	NICHD	NICHD	The University of Utah
Centers of Excellence for Influenza Research and Surveillance (CEIRS) Reagent Resources	NIAID	NIAID	NIAID
Central Africa International Epidemiologic Databases to Evaluate AIDS (IEDEA)	NIAID	NIAID, NCI, NICHD, NIMH, NIDA	Research Triangle Institute
ChemDB HIV, Opportunistic Infection and Tuberculosis Therapeutics Database (ChemDB)	NIAID	NIAID	NIAID
Chemical Carcinogenesis Research Information System (CCRIS)	NLM	NLM	NLM
Chemical Effects in Biological Systems	NIEHS	NIEHS	NIEHS
Chemical Environment (ICE)	NIEHS/NTP	NIEHS/NTP	NICEATM partners
Chemical Hazards Emergency Medical Management (CHEMM)	NLM	NLM	NLM
ChemIDplus	NLM	NLM	NLM
Childhood Liver Disease Research Network	NIDDK	NIDDK	Multiple
China Health and Retirement Longitudinal Study	NIA	NIA	Peking University
Chronic Kidney Disease in Children (CKiD) Study	NIDDK	NIDDK, NICHD, NHLBI	Multiple

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Chronic Renal Insufficiency Cohort (CRIC) Study	NIDDK	NIDDK	Multiple
Cistrome	NCI	NCI	Dana–Farber Cancer Institute
Classification of Laws Associated with School Students	NCI	NCI	NCI
ClinGen	NHGRI	NHGRI, NICHD, NCI	Multiple
Clinical Proteomic Tumor Analysis Consortium (CPTAC) Antibody Portal	NCI	NCI	Leidos
Clinical Proteomic Tumor Analysis Consortium (CPTAC) Assay Portal	NCI	NCI	ESAC, Inc.
Clinical Proteomic Tumor Analysis Consortium (CPTAC) Data Portal	NCI	NCI	ESAC, Inc.
Clinical Proteomic Tumor Analysis Consortium (CPTAC) Huddle	NCI	NCI	Huddle
Clinical Research Study Investigators' Toolbox	NIA	NIA	NIA
Clinical Trial Reporting Program (CTRP)	NCI	NCI	Multiple
Clinical Trials Dissemination Library	NIDA	NIDA	Washington University
Clinical Trials Public Data Share Website	NIDA	NIDA	NIDA
Clinical Trials Support Unit Enterprise (CTSU-ESYS)	NCI	NCI	NCI
Clinically Relevant Genetic Variants Resource	NHGRI	NHGRI, NICHD	The University of North Carolina and Stanford
ClinicalTrials.gov	NLM	NLM	NLM
ClinVar	NLM	NLM	NLM
Clone DB	NLM	NLM	NLM
Clusters of Orthologous Groups (COGS)	NLM	NLM	NLM
CNV (Copy Number Variation) Atlas of Human Development	OD	NICHD	Emory University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Cohort Metadata Repository (CMR)	NCI	NCI	NCI
Collaborative Health Outcomes Information Registry (CHOIR)	NIDA	NIDA, NIA, NINR, NEI, NINDS	Stanford Medical School
Collaborative Initiative on Fetal Alcohol Spectrum Disorders - Informatics Core	NIAAA	NIAAA	Indiana University, Bloomington
Collaborative Islet Transplant Registry (CITR)	NIDDK	NIDDK	EMMES Corp.
Collaborative Pediatric Critical Care Research Network (CPCCRN) Datasets	NICHD	NICHD	The University of Utah
Collaborative Studies on Genetics of Alcoholism (COGA) Database	NIAAA	NIAAA	SUNY Downstate Medical Center
Colorectal Cancer Mortality Projections	NCI	NCI	NCI
COMBINE (Combining Medications and Behavioral Interventions) Data Set	NIAAA	NIAAA	NIAAA
Comparative Toxicogenomics Database (CTD)	NIEHS	NIEHS, NLM	Mount Desert Island Biological Lab
Computer Access to Research on Dietary Supplements (CARDS) Database	OD/ODS	OD/ODS	OD/ODS
Conexion: A Localized Information Resource for a Low-Income Hispanic Community	NLM	NLM	Columbia University Health Sciences
Connectome Coordination Facility	NIMH	NIH Blueprint	Washington University
Consensus Coding Sequence Regions (CCDS) Database	NLM	NLM	NLM
Conserved Domain Database (CDD)	NLM	NLM	NLM
Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer	NIDDK	NIDDK, NCI	Multiple
Consortium on Interplay of Genes and Environment across Multiple Studies	NIA	NIA	Multiple
Consortium on Safe Labor	NICHD	NICHD	NICHD, NIH
Consortium on Safe Labor Tuberculosis Portals	NIAID, NICHD	NIAID, NICHD	NIAID, NIH

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Coordinating and Bioinformatics Unit for the DCC/MMPC (Diabetic Complications Consortium/Mouse Metabolic Phenotyping Centers)	NIDDK	NIDDK	Georgia Regents University
Coupling Results Data from ClinicalTrials.gov and Biblio-graphic Databases to Accelerate Evidence Synthesis	NLM	NLM	Boston Children's Hospital
CRCNS Data Sharing: Exchange and Evaluation of Reduced Neuron Models	NIBIB	NIBIB	Arizona State University, Tempe
Critical Care Informatics	NIBIB	NIBIB	MIT
Cure Glomerulonephropathy (CureGN) Network	NIDDK	NIDDK	Multiple
Cytogenetic and Down Syndrome Models Resource	NICHD	NICHD	The Jackson Laboratory
Cytogenetic Models Resource for Chromosomal Disorders	NICHD	NICHD	The Jackson Laboratory
DailyMed	NLM	NLM	NLM
Data Archive and Specimen Hub (DASH)	NICHD	NICHD	NICHD
Data Archive BRAIN Initiative (DABI)	NIMH	NINDS	University of Southern California
Data Management and Coordinating Center (DMCC)	NCATS	NCATS	University of South Florida
Data Sharing for Demographic Research	NICHD	NICHD	University of Michigan
Data Structures, Algorithms and Tools for Ontological Discovery	NIAAA	NIAAA	The Jackson Laboratory
Database for Annotation, Visualization, and Integrated Discovery (DAVID)	NIAID	NIAID	NIAID
Database of Expressed Sequence Tag Records (dbEST)	NLM	NLM	NLM
Database of Genome Survey Sequences (dbGSS)	NLM	NLM	NLM
Database of Genomic Structural Variation (dbVar)	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Database of Genotypes and Phenotypes (dbGaP)	NLM	NLM	NLM
Database of Longitudinal Studies	NIA	NIA	NIA
Database of Short Genetic Variations (dbSNP)	NLM	NLM	NLM
Databrary	NICHD	NICHD, NSF	New York University, The Pennsylvania State University
Deciphering Cellular Signaling System by Deep Mining a Comprehensive Genomic Compendium	NLM	NLM	University of Pittsburgh at Pittsburgh
Decision Support System for Temporal Lobe Epilepsy	NIBIB	NIBIB	Henry Ford Health System
Decision-Making Modeling for Treating Intimate Partner Violence	NLM	NLM	Case Western Reserve University
Deconvolution of Epigenomic Data to Characterize Cellular Subpopulations	NLM	NLM	Washington University
Deep and Integrative Analysis of RNA Sequencing Data to Identify Pathogenesis Heterogeneity of Chronic Lung Disease	NLM	NLM	Yale University
Deep Learning for Protein Subcellular/Sub-organelle Localizations and Localization Motifs	NLM	NLM	University of Missouri, Columbia
Deep Learning for Pulmonary Embolism Imaging Decision Support: A Multi-institutional Collaboration	NLM	NLM	Stanford University
Deep Phenotyping in Electronic Health Records for Genomic Medicine	NLM	NLM	Columbia University Health Sciences
DeepSeeNet: A Deep Learning Model for Automated Classification of Patient-Based Age-Related Macular Degeneration Severity from Color Fundus Photographs	NLM, NEI	NLM, NEI	NLM, NEI
Demystifying Biomedical Big Data: A User's Guide	NLM	NLM	Georgetown University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Developing and Applying Information Extraction Resources and Technology to Create	NLM	NLM	University of Colorado Denver
Developing Graph Models and Efficient Algorithms for the Study of Cancer Disease	NLM	NLM	University of Pittsburgh at Pittsburgh
Development and Application of Phenome-wide Scan of Heritability (PheSH)	NLM	NLM	Marshfield Clinic Research Foundation
Development and Evaluation of a Learning Electronic Medical Record System	NLM	NLM	University of Pittsburgh at Pittsburgh
Development of a Best Practices in Research Data Management Massive Open Online Course (MOOC)	NLM	NLM	Harvard Medical School
Development of an Infertility Family Research Registry (IFRR)	NICHD	NICHD	Dartmouth College
Development of dictyBase, an Online Informatics Resource	NIGMS	NIGMS	Northwestern University
Developmental and Reproductive Toxicology Database (DART)	NLM	NLM	NLM
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)	NIDDK	NIDDK	Multiple (NIDDK, DCC)
Diabetes Prevention Program Outcomes Study (DPPOS)	NIDDK	NIDDK	Multiple (The George Washington University, DCC)
Dietary Supplement Ingredients Database	OD/ODS	OD/ODS	OD/ODS, FDA, USDA
Dietary Supplement Label Database	NLM	ODS, NLM	ODS
Digital Collections	NLM	NLM	NLM
Digitized Atlas of Mouse Liver Lesions	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
Disaster Lit: Resource Guide for Disaster Medicine and Public Health	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Disaster Research Response (DR2) Data Collection Tools	NLM	NLM, NIEHS	NLM, NIEHS, CDC, Center for Research on the Epidemiology of Disasters, NIOSH
Discovering and Applying Knowledge in Clinical Databases	NLM	NLM	Columbia University Health Sciences
Disease Emergence and Elimination: Using Mobility Data to Inform Spatial Disease Dynamics	NLM	NLM	Johns Hopkins University
Disorders of Sex Development Network Patient Registry	NICHD	NICHD	UCLA
Distance-Based Panomic Analytics for Microbiome Data	NLM	NLM	Medical University Of South Carolina
Drug Information Portal	NLM	NLM	NLM
Drug-Induced Liver Injury Network (DILIN) Retrospective Study (ILIAD)	NIDDK	NIDDK	Multiple
DrugMatrix	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
DS-Connect™: The Down Syndrome Registry	NICHD	NICHD	NIH
Early Detection Research Network (EDRN)	NCI	NCI	Multiple
East Africa IeDEA Regional Consortium	NIAID	NIAID, NCI, NICHD, NIMH, NIDA	Indiana University
eMERGE Data Commons	NHGRI	NHGRI	Baylor College of Medicine
ENCODE Data Coordinating Center	NHGRI	NHGRI	Stanford University
Endometrium Database Resource	NICHD	NICHD	University of California, San Francisco
English Longitudinal Study of Ageing	NIA	NIA	University College London
Enhanced Echinobase	NICHD	NICHD, NHGRI, NCATS	Baylor College of Medicine
Environmental Health Economic Analysis Annotated Bibliography	NIEHS	NIEHS	NIEHS

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Environmental Polymorphisms Registry (EPR)	NIEHS	NIEHS	Integrated Laboratory Systems, Inc., and The University of North Carolina
Epigenome Browser	NHGRI	NHGRI	Washington University
Epigenomics/NIH Roadmap Epigenomics Project Data Listings	NLM	NLM	NLM
eRA Portfolio Visualization (P-VIZ)	OER	OD	NIH
Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)	OER	OD	NIH
Eukaryotic Pathogen Database Resources (EuPathDB)	NIAID	NIAID	University of Pennsylvania
Expression Quantitative Trait Loci (eQTL) database	NHLBI, NLM, CIT	NHLBI, NLM, CIT	NHLBI, CIT, NLM, Boston University
ExRNA Research Portal	NIDA	OD/OSC (Common Fund)	Baylor University
exRNA Virtual Repository	NIDA	OD/OSC (Common Fund)	Baylor College of Medicine
eyeGENE	NEI	NEI	NEI
eyeIntegration	NEI	NEI	NEI
FaceBase: A Resource for Craniofacial Researchers	NIDCR	NIDCR	University of Southern California
Family Life, Activity, Sun, Health, and Eating (FLASHE) study	NCI	NCI	NCI
Finding Cancer Statistics	NCI	NCI	NCI
FITBIR (Federal Interagency Traumatic Brain Injury Research) Informatics System	NINDS	NINDS, DoD	NIH CIT
FluOMICS: The NEXT Generation	NIAID	NIAID	Icahn School of Medicine at Mount Sinai

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
FLYBASE: A Drosophila Genomic and Genetic Database	NHGRI	NHGRI	Harvard University
Food Attitudes and Behavior Survey Project	NCI	NCI	NCI
Fragile Families and Child Wellbeing Study	NICHD	NICHD	Princeton University
Fungal and Oomycete Genomics Resources (FungiDB)	NIAID	NIAID	University of Georgia
Gabriella Miller Kids First Pediatric Research Program	NICHD, NCI	OD/OSC (Common Fund)	NIH
GARD	NCATS	NCATS, NHGRI	ICF
Gastroparesis Registry 2, Gastroparesis Clinical Research Consortium (GpCRC)	NIDDK	NIDDK	Multiple
Gateway to Global Aging Data	NIA	NIA	University of Southern California
Geisha, A Chicken Embryo Gene Expression Resource	NICHD	NICHD	The University of Arizona
GenBank	NLM	NLM	NLM
GENCODE: Comprehensive Gene Annotation for Human and Mouse	NHGRI	NHGRI	Sanger Institute
Gene	NLM	NLM	NLM
Gene Expression Database for Mouse Development	NICHD	NICHD	The Jackson Laboratory
Gene Expression Nervous System Atlas (GENSAT)	NINDS	NINDS	The Rockefeller University
Gene Ontology Consortium	NHGRI	NHGRI, NIGMS	University of Southern California
GeneNetwork	NIAAA	NIAAA, NIGMS, NIDA, NIA, NCI	The University of Tennessee Health Sciences Center
Genes and Disease	NLM	NLM	NLM
Genetic Testing Registry (GTR)	NLM	NLM, OD	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Genetic Toxicology Databank (GENE-Tox)	NLM	NLM	EPA
Genetics Home Reference	NLM	NLM	NLM
GenitoUrinary Development Molecular Anatomy Project (GUDMAP)	NIDDK	NIDDK	The University of Edinburgh
Genome	NLM	NLM	NLM
GenomeSpace: Community Web Environment for Analysis across Diverse Genomic Tools	NHGRI	NHGRI	University of California, San Diego
Genomic Database for Candida Albicans	NIDCR	NIDCR	Stanford University
Genomic Database for the Yeast Saccharomyces	NHGRI	NHGRI	Stanford University
Genomic Resources for the Collaborative Cross	NHGRI	NHGRI	The University of North Carolina
Genomics and Bioinformatics Software Tools	NCI	NCI	NCI
Genomics Resources for the Collaborative Cross	NHGRI	NHGRI	The University of North Carolina
Genotype-Tissue Expression (GTEx) Portal	NHGRI	OD/OSC (Common Fund)	Broad Institute of MIT and Harvard
GEO (Gene Expression Omnibus)	NLM	NLM	NLM
Glioblastoma Bio Discovery Portal	NCI	NCI	NCI
Global Ingredient Archival System (GINAS)	NCATS	NCATS	NCATS
Global Rare Diseases Registry Data Repository/GRDR^{R}	NCATS	NCATS	NCATS
Globus Genomics	NHGRI	NHGRI	The University of Chicago
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)	NIDDK	NIDDK	Multiple
Glycomics/Legacy Informatics Resources for Glycomics	NIGMS	NIGMS	MIT

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Graphic Medicine: Ill-Conceived and Well-Drawn	NLM	NLM	NLM
Grid-Enabled Measures	NCI	NCI	NCI
H3ABioNet: A Sustainable African Bioinformatics Network for H3Africa	NHGRI	OD/OSC (Common Fund)	University of Cape Town
Harmonizome	NCI	OD/OSC (Common Fund)	Mount Sinai
Hazardous Substances Data Bank (HSDB)	NLM	NLM	NLM
Haz-Map: Information on Hazardous Chemicals and Occupational Diseases	NLM	NLM	NLM
HD*Pulse* Data Portal	NIMHD	NIMHD	NIMHD
Health and Retirement Study	NIA	NIA	University of Michigan
Health Disparities Calculator (HD*Calc)	NCI	NCI	NCI
Health Information National Trends Survey	NCI	NCI	NCI
Health Services and Sciences Research Resources Database (HSRR)	NLM	NLM	NLM
Health Services Research Projects in Progress (HSRProj) Database	NLM	NLM	NLM
Health Services/Technology Assessment Text (HSTAT)	NLM	NLM	NLM
HealthReach	NLM	NLM	NLM
Hemagglutinin Structure Prediction Server (HASP)	NIAID	NIAID	NIAID
Hepatitis B Research Network: Observational Databases in Adults and Children	NIDDK	NIDDK	Multiple
Hereditary Causes of Nephrolithiasis and Kidney Failure	NIDDK	NIDDK	Mayo Clinic Rochester

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Histone Database: HistoneDB 2.0 – with variants and MS_HistoneDB	NLM	NLM	NLM
HIV Molecular Immunology Database	NIAID	DOE, NIAID	Los Alamos National Laboratory
HIV Protein Interaction Database	NIAID	NLM, NIAID	DAIDS/NIAID and NLM
HIV Sequence Database	NIAID	DOE, NIAID	Los Alamos National Laboratory
HIV/AIDS Cancer Match Study	NCI	NCI	NCI
HIV-1 resistance mutation database	NIAID	DOE, NIAID	Los Alamos National Laboratory
HIV-1, Human Interaction Database	NLM	NIAID, NLM	NLM
HomoloGene	NLM	NLM	NLM
Household Products Database	NLM	NLM	NLM
Human "Brain Bank" Tissue for Alcohol Research	NIAAA	NIAAA	The University of Sydney
Human Biological Data Interchange	NIDDK	NIDDK	National Disease Research Interchange (NIDDK and others)
Human DNA Polymerase Gamma Mutation Database	NIEHS	NIEHS	NIEHS
Human Epigenome Atlas	NIEHS, NIDA, NIDCD	OD/OSC (Common Fund)	Multiple, see http://www.roadmapepigenomics.org/participants
Human Islet Research Network (HIRN)	NIDDK	NIDDK	Multiple
Human Microbiome Project Data Analysis and Coordination Center Data Portal	NHGRI	OD/OSC (Common Fund)	University of Maryland, Baltimore
Human Oral Microbiome Database (HOMD)	NIDCR	NIDCR	The Forsyth Institute
Human Pancreas Analysis Program	NIDDK	NIDDK	University of Pennsylvania

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
IeDEA West-Africa Collaboration	NIAID	NIAID, NCI, NICHD, NIMH, NIDA	Association for the Development of Teaching and Research in Aquitaine (ADERA)
Images from the History of Medicine	NLM	NLM	NLM
ImmPort	NIAID	NIAID	Northrup Grummon
Immune Epitope Database and Analysis Program	NIAID	NIAID	La Jolla Institute for Allergy & Immunology
Immune Polymorphism Database/Major Histocompatibility Complex of Non-Human Primates	NIAID	NIAID	European Molecular Biology Laboratory/European Bioinformatics Institute
ImmuneSpace (Human Immunology Project Consortium [HIPC] database)	NIAID	NIAID	Fred Hutchinson Cancer Research Center
Inferred Biomolecular Interactions Server (IBIS)	NLM	NLM	NLM
Influenza Dynamic Network Modeling Project (FluDyNeMo)	NIAID	NIAID	New York University
Influenza Research Database	NIAID	NIAID	Northrup Grumman Health IT, J. Craig Venter Institute
Influenza Virus Resource/Influenza Virus Database	NLM	NLM	NLM
Informatics for Integrating Biology to the Bedside (i2b2)	NIMHD	NIMHD	Jackson State University, University of Puerto Rico Medical Sciences Campus, Morehouse School of Medicine
Informatics for Integrative Brain Tumor Whole Slide Analysis	NLM	NLM	Emory University
Inherited Bone Marrow Failure Syndromes	NCI	NCI	NCI
InSPECt: Interactive Surveillance Portal for Evaluating Clinical Support	NLM	NLM	Tulane University of Louisiana
Instruments to Detect Cognitive Impairment in Older Adults	NIA	NIA	NIA

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Integrated Chemical Environment (ICE)	NIEHS/NTP	NIEHS/NTP	NICEATM Partners
Integrated Risk Information System (IRIS)	NLM	NLM, EPA	NLM
Integrative Analysis of Longitudinal Studies on Aging	NIA	NIA	Oregon Health & Science University
Integrative Neuroscience Initiative on Alcoholism Neuroimmune (INIA-N) Consortia	NIAAA	NIAAA	The University of Texas at Austin
Integrative Neuroscience Initiative on Alcoholism Stress (INIA-Stress) Consortia Neuroimmune (INIA-N) Consortia	NIAAA	NIAAA	Oregon Health & Science University
Interagency Registry for Mechanically Assisted Circulatory Support	NHLBI	NHLBI	The University of Alabama at Birmingham
International Epidemiologic Databases to Evaluate AIDS-Southern Africa (IeDEA-SA)	NIAID	NIAID, NCI, NICHD, NIMH, NIDA	University of Bern
International Myositis Assessment & Clinical Studies Group (IMACS) Outcomes Repository	NIEHS	NIEHS	NIEHS
International Registry of Werner Syndrome	NIA	NCI, NIA	University of Washington
International Research Registry Network for Sjögren's Syndrome	NIDCR	NIDCR	University of California, San Francisco
International Skeletal Dysplasia Registry	NICHD	NICHD	University of California, Los Angeles
International Toxicity Estimates for Risk (ITER)	NLM	NLM	TERA
IOBIO: Online Visualization Tool for Genomic Data	NHGRI	NHGRI	The University of Utah
Irish Longitudinal Study on Aging	NIA	NIA	Trinity College, Dublin
Japanese Study of Aging and Retirement	NIA	NIA	Research Institute of Economy, Trade, and Industry; Hitotsubashi University; and University of Tokyo

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
KOMP2 Data Coordination Center	NHGRI	OD/OSC (Common Fund), NHGRI, NIGMS	European Molecular Biology Laboratory
Korean Longitudinal Study of Aging	NIA	NIA	Korea Labor Institute
LactMed (Drugs and Lactation Database)	NLM	NLM	NLM
Library of Integrated Network-based Cellular Signatures (LINCS)	NHLBI/NHGRI	OD/OSC (Common Fund)	Multiple
Liver Tissue and Cell Distribution System	NLM	NLM	University of Minnesota
LiverTox (Database of clinical and research information on drug-induced liver injury)	NIDDK, NLM	NIDDK, NLM	NIDDK, NLM
LogOddsLogo program for analysis of DNA and protein sequences	NLM	NLM	NLM
Longitudinal Aging Study in India	NIA	NIA	Harvard T.H. Chan School of Public Health
Longitudinal Study of Adolescent Health Behavior (NEXT Study)	NICHD	NICHD	NICHD, NIH
LONI (Laboratory of Neural Imaging) Image Data Archive	NIBIB	NIBIB	University of Southern California
Lupus Family Registry	NIAMS	NIAMS	Oklahoma Medical Research Foundation
Malaria Host-Pathogen Interaction Center	NIAID	NIAID	Emory University
Maternal Fetal Medicine Units Data Coordinating Center	NICHD	NICHD	The George Washington University
Maternal Newborn Health Registry of the Global Network for Women's and Children's Health Research	NICHD	NICHD	Research Triangle Institute
MedlinePlus	NLM	NLM	NLM
Meeting Clinicians' Information Needs with Highly Tailored Knowledge Summaries	NLM	NLM	The University of Utah

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Metabolomics Workbench	NIDDK	OD/OSC (Common Fund)	University of California, San Diego
Mexican Health and Aging Study	NIA	NIA	University of Pennsylvania, University of Maryland, University of Wisconsin, and the Instituto Nacional de Estadística, Geografía e Informática (INEGI) in Mexico
MH-GRID – Minority Health Genomics and Translational Research Database	NIMHD	NIMHD	Morehouse School of Medicine
Microphysiological Systems Data Center	NCATS	NCATS	University of Pittsburgh
Midlife in the United States	NIA	NIA	University of Wisconsin
Miner Suite of Bioinformatic Software Packages	NCI	NCI	NCI
Molecular Modeling Database (MMDB)	NLM	NLM	NLM
Monitoring the Future (MTF)	NIDA	NIDA	University of Michigan
Morehouse Healthcare Personalized (P4) Health for Women	NIMHD	NIMHD	Morehouse School of Medicine
Mouse Genome Database	NHGRI	NHGRI	The Jackson Laboratory
Mouse Tumor Database	NCI	NCI	The Jackson Laboratory
MPI Bioinformatics Toolkit with a New HHpred Server for the Advanced Bioinformatic Analysis of Proteins	NLM	NLM	Max Planck Institute for Developmental Biology and NLM
MSigDB	NCI	NCI	Broad Institute
Multicenter AIDS Cohort Study (MACS) Public Data Set	NIAID	NIAID, NCI, NIDA, NIMH, NHLBI	Johns Hopkins University, Northwestern University, University of California Los Angeles, University of Pittsburgh
Multidisciplinary Approach to the Study of Pelvic Pain (MAPP) Research Network	NIDDK	NIDDK	Multiple (University of Pennsylvania, DCC)

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Mutant Mouse Resource and Research Centers Informatics, Coordination and Service Center	OD/ORIP	OD/ORIP	University of California Davis
MutSpliceDB: A Database of Splice Sites Variants	NCI	NCI	NCI
Nanomaterial Registry	NIBIB	NCI	RTI International
National Addiction & HIV Data Archive Program	NIDA	NIDA	University of Michigan
National Alzheimer's Coordinating Center	NIA	NIA	University of Washington
National Archive of Computerized Data on Aging	NIA	NIA	National Archive of Computerized Data on Aging (ICPSR)
National Cell Repository for Alzheimer's Disease (NCRAD)	NIA	NIA	University of Indiana
National Clinical Trials Network Data Archive	NCI	NCI	Alliance for Clinical Trials in Oncology, Canadian Cancer Trials Group, Children's Oncology Group, ECOG-ACRIN Cancer Research Group, NRG Oncology, Southwest Oncology Group
National Consortium on Alcohol & Neurodevelopment in Adolescence	NIAAA	NIAAA	SRI International
National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	NIAAA	NIAAA	NIAAA
National Health and Aging Trends Study	NIA	NIA	Johns Hopkins University
National Health and Nutrition Examination Survey	NCI	Multiple	National Center for Health Statistics (NCHS), CDC

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
National Health and Nutrition Examination Survey 2019–2020, Nutrition Questionnaire Component for Survey Participants Age 0 Up to 24 Months	NICHD	NICHD, CDC	CDC
National Health Interview Survey — Cancer Control Supplement	NCI	NCI, CDC	NCHS, CDC
National Health Interview Survey -Use of Complementary and Integrative Health Approaches Supplement	NCCIH	NCCIH	NCHS, CDC
The National Institutes of Health Research Portfolio Online Reporting Tools (RePORT)	OER	OD	NIH
National Long-Term Care Survey	NIA	NIA	Duke University
National Neuro AIDS Tissue Consortium	NIMH	NIMH, NINDS	The University of Texas Medical Branch University of California, San Diego; Reed Neurological Research Center; Mount Sinai Medical Center; EMMES Corp.; and University of Nebraska
National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members	NHLBI	NINDS	University of Rochester
National Social Life, Health, and Aging Project	NIA	NIA	The University of Chicago
NCATS Inxight: Drugs	NCATS	NCATS	NCATS
NCATS Pharmaceutical Collection	NCATS	NCATS	NCATS
NCI Brain Neoplasia Data at Georgetown Database of Cancer (G-DOC)	NCI	NCI	Georgetown University
NCI Genomics Data Commons	NCI	NCI	NCI
NCI Transcriptional Pharmacodynamics Workbench	NCI	NCI	NCI
NCTN/NCORP Data Archive	NCI	NCI	NCI

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
NDEx	NCI	NCI	University of California, San Diego
NEI Commons	NEI	NEI	NEI
NEI Data Commons	NEI	NEI	NEI
NEI NGS Data	NEI	NEI	NEI
NEIBANK: EST Analysis and Bioinformatics for Ocular Genomics	NEI	NEI	NEI
Neonatal Research Network Data Coordinating Center	NICHD	NICHD	Research Triangle Institute
Nephrotic Syndrome Study Network (NEPTUNE)	NIDDK	NIDDK	Multiple (University of Michigan, DCC)
Neurobiology of Adolescent Drinking in Adulthood (NADIA)	NIAAA	NIAAA	The University of North Carolina at Chapel Hill
Neurodata Without Borders: Neurophysiology (NWB:N) Data Format	NIMH	NIMH, NINDS	Lawrence Berkeley National Laboratory
Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC)	NIBIB	NIBIB, NEI, NIA, NIAAA, NICHD, NIDA, NIDCR, NIMH, NINDS, NINR	Turner Consulting Group, Inc.
NeuroQOL: Quality of Life Outcomes Instrument for CNS Diseases	NINDS	NINDS	Northwestern University Feinberg School of Medicine
Newborn Screening Translational Research Network (Clinical Laboratory Performance Repository, Virtual Repository of Dried Blood Spots, Longitudinal Pediatric Data Source)	NICHD	NICHD	NICHD, NIH
NewDrugTargets.org	NCI	OD/OSC (Common Fund)	The University of New Mexico
NHLBI Biologic Specimen Repository	NHLBI	NHLBI	Precision Bioservices
NIA Genetics of Alzheimer's Disease Data Storage Site	NIA	NIA	University of Pennsylvania

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
NIA Primate Aging Database	NIA	NIA	University of Wisconsin–Madison
NIDA Center for Genetics Research	NIDA	NIDA	Rutgers, the State University of New Jersey, with subcontract to Washington University in St. Louis
NIDCD National Temporal Bone, Hearing, and Balance Pathology Resource Registry	NIDCD	NIDCD	Massachusetts Eye and Ear Infirmary
NIDDK Central Repository: Bio Repository	NIDDK	NIDDK	Precision for Medicine
NIDDK Central Repository: Data Repository	NIDDK	NIDDK	Information Management Services, Inc.
NIDDK Inflammatory Bowel Disease Genetics Consortium Repository Database	NIDDK	NIDDK	Icahn School of Medicine at Mount Sinai
NIDDK Information Network (dkNET)	NIDDK	NIDDK	University of California, San Diego
NIH Blueprint Neuroscience Information Framework	NIDA	NIBIB, NCCIH, NEI, NIA, NIAAA, NICHD, NIDA, NIDCR, NIEHS, NIMH, NINDS, NINR	University of California, San Diego
NIH Chest X-ray Image Datasets	NLM, CC	NLM, CC	NLM, CC, Indiana University
NIH Common Data Elements (CDE) Repository	NLM	NLM	NLM
NIH Human Embryonic Stem Cell (hESC) Registry	OSP/OD	OSP/OD	OSP/OD

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
NIH NeuroBioBank	NIMH	NICHD, NIMH, NINDS	NIH, University of Miami Brain Endowment Bank; University of Maryland Brain and Tissue Bank; Harvard Brain Tissue Resource Center; The Human Brain and Spinal Fluid Resource Center; Mount Sinai Brain Bank; and University of Pittsburgh Brain Tissue Donation Program
NIH Roadmap Epigenomics Project Data Listings	NLM	NLM	NLM
NIH Stem Cell Data Management System	NINDS	NINDS	NIH Stem Cell Unit and NINDS Division of Intramural Research
NIH Tetramer Core Facility	NIAID	NIAID	Emory/Yerkes
NIMH Chemical Synthesis and Drug Supply Program	NIMH	NIMH	RTI International
NIMH Data Archive	NIMH	NIMH, NICHD, NIEHS, NINDS, NIAMS, NIAAA	NIMH, NIH
NIMH Human Brain Collection Core	NIMH	NIMH	NIMH
NIMH Repository and Genomics Resource	NIMH	NIMH	Washington University in St. Louis; Rutgers the State University of New Jersey; University of Southern California
NINDS Common Data Elements	NINDS	NINDS	KAI Research, Inc.
NINDS Human Cell and Data Repository	NINDS	NINDS	Rutgers, the State University of New Jersey
NINDS Human Genetics Resource Center	NINDS	NINDS	Coriell Institute for Medical Research
NINDS/UC Davis NeuroMab Facility	NINDS	NINDS, NIMH, OD, NCATS	University of California, Davis

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
NLM Catalog	NLM	NLM	NLM
NLM Scrubber Software Tool for Computationally De-Identifying Clinical Documents	NLM	NLM	NLM, CC, NCI
NNLM *All of Us* Community Engagement Network	NLM, OD	NLM, OD	NLM, OD
NNLM RD3 - Resources for Data-Driven Discovery	NLM	NLM	NLM
Nomenclature of Human and Vertebrate Genes	NHGRI	NHGRI	European Molecular Biology Laboratory
Nonalcoholic Steatohepatitis Clinical Research Network's Nonalcoholic Fatty Liver Disease (NAFLD) Database (Adult and Pediatric)	NIDDK	NIDDK	Multiple
Nonhuman Primate HIV/SIV Vaccine Trials Database	NIAID	DOE, NIAID	Los Alamos National Laboratory
Nonneoplastic Lesion Atlas	NTP	NIEHS/NTP	NTP
North American AIDS Cohorts Collaboration on Research and Design (IeDEA)	NIAID	NIAID, NCI, NICHD, NIMH, NIDA	Johns Hopkins University
Novel Markers of Prognosis in Hypertrophic Cardiomyopathy (HCMR)	NHLBI	NHLBI	University of Virginia
NTP Historical Control Database	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
Nucleotide	NLM	NLM	NLM
Object Color Statistics	NEI	NEI	NEI
Observational Antiretroviral Studies in Southern Africa (OASIS) Collaboration	NIAID	NIAID	University of Bern, Switzerland
Ocular Proteome	NEI	NEI	NEI
Omics for TB: Response to Infection and Treatment	NIAID	NIAID	Seattle Children's Hospital
Omics of Lethal Human Viruses	NIAID	NIAID	University of Wisconsin–Madison

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
OmniSearch	NCI	NCI	University of South Alabama
Online Mendelian Inheritance in Animals (OMIA)	NLM	NLM	NLM
Online Mendelian Inheritance in Man (OMIM)	NHGRI	NHGRI	Johns Hopkins University
Open-i – Image/Text Search System	NLM	NLM	NLM
OpenNeuro Data Archive	NIMH	NINDS	Stanford University
OptiRNAi 2.0	NCI	NCI	NCI
ORIO: Online Resource for Integrative Omics	NIEHS	NIEHS	NIEHS
Orthopedic image dataset	NLM	NLM	University of Southern California
Osteoarthritis Initiative (OAI) Data Coordination Center	NIAMS	NIBIB, NIA, ORWH	University of California, San Francisco
Panel Study of Income Dynamics	NIA	NIA	University of Michigan
Papillomavirus Episteme (PaVE)	NIAID	NIAID	NIAID
Parkinson's Disease Biomarkers Program (PDBP) Database and Repository	NINDS	NINDS	NINDS
Pathogen Detection Project and Pathogen Detection Isolates Browser	NLM	NLM	NLM, CDC, FDA, USDA, Public Health England, Association of Public Health Laboratories
PathoSystems Resource Integration Center (PATRIC)	NIAID	NIAID	The University of Chicago
Pathway Commons: A Public Library of Biological Pathways	NHGRI	NHGRI	Harvard Medical School
Pathway Interaction Database Support	NCI	NCI	NCI
Pediatric Imaging, Neurocognition, and Genetics (PING)	NIDA	NIDA	University of California, San Diego
Pediatric Myelodysplastic Syndrome and Bone Marrow Failure Patient Registry	NIDDK	NIDDK	Children's Hospital Corporation, Boston

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Pharmacogenomics Knowledge Base (PharmGKB)	NIGMS	NIGMS	Stanford University
PHAROS	NCI	OD/OSC (Common Fund)	The University of New Mexico
Phenotype-Genotype Integrator (PheGenI), merges NHGRI genome-wide association study (GWAS) catalog data with several databases housed at NLM	NLM, NHGRI	NLM, NHGRI	NLM, NHGRI, Broad Institute
PhenX Toolkit	NHGRI	NHGRI, NIDA, NHLBI, NIMHD, OD	Research Triangle Institute
Physical Sciences-Oncology Network Bioresource Core Facility (PBCF)	NCI	NCI	ATCC
Physical Sciences-Oncology Network Data Coordinating Center (PS-ON DCC)	NCI	NCI	NCI
Pillbox	NLM	NLM	NLM
Placental Atlas Tool	NICHD	NICHD	NIH
Pleuropulmonary Blastoma DICER1 Syndrome Study	NCI	NCI	The International Pleuropulmonary Blastoma Registry; The International Ovarian and Testicular Stromal Tumor Registry; Children's Hospital, Washington, DC; and St. Louis Children's Hospital
PopSet	NLM	NLM	NLM
PorA VR3 Typing Database	NIAID	NIAID	NIAID
Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT Study)	NIDDK	NIDDK	Connecticut Children's Medical Center
PregSource	NICHD	NICHD	Multiple
Prevention of Renal Damage in Primary Hyperoxaluria	NIDDK	NIDDK	Mayo Clinic Rochester

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
PRISMS Informatics Platform – Federated Integration Architecture	NIBIB	NIBIB	The University of Utah
PRISMS: Data and Software Coordination and Integration Center (DSCIC)	NIBIB	NIBIB	USC
Probe	NLM	NLM	NLM
Probe Database (a public registry of nucleic acid reagents)	NLM	NLM	NLM
Profiles in Science	NLM	NLM	NLM
Project MATCH Data Base	NIAAA	NIAAA	University of Connecticut Health Center
Prostate Cancer Prevention Trial (PCPT) Biorepository	NCI	NCI	Southwest Cooperative Oncology Group (SWOG)
PLCO: Etiology and Early Marker Studies	NCI	NCI	NCI
Protein	NLM	NLM	NLM
Protein Clusters	NLM	NLM	NLM
Protein Data Bank	NSF	DOE, NIGMS, NLM, NSF, NCI	Rutgers, the State University of New Jersey; and University of California, San Diego
Protein Database (collection of sequences from several sources)	NLM	NLM	NLM
PROWL	NEI	NEI	NEI, FDA
PubChem	NLM	NLM	NLM
Public HIV Drug Resistance Database	NIAID	NIAID	Stanford University
PubMed Central	NLM	NLM	NLM
PubMed/Medline	NLM	NLM	NLM
Radiation Emergency Medical Management (REMM)	NLM	NLM	NLM
Rare Diseases Data Management and Coordinating Center (DMCC)	NCATS	NCATS	University of South Florida

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Rat Genome Database	NHLBI	NHLBI, NCI, NEI, NHGRI, NIA, NIAAA, NICHD, NIDDK, NIMH, NINDS	Medical College of Wisconsin
RDCRN Data Management and Coordinating Center	NCATS	NCATS	University of South Florida
Reactome: An Open Knowledgebase of Human Pathways	NHGRI	NHGRI	Coriell Institute for Medical Research
Reference Sequence Database (RefSeq)	NLM	NLM	NLM
Registry and Surveillance for Hemoglobinopathies	NHLBI	NHLBI	CDC
Registry for Eosinophilic Gastrointestinal Disorders, Consortium of Eosinophilic Gastrointestinal Disease Researchers, Rare Diseases Clinical Research Network	NIAID	NIAID, NIDDK, NCATS	Multiple (Cincinnati Children's Hospital Medical Center, DCC)
RegulomeDB: A Resource for the Human Regulome	NHGRI	NHGRI	Stanford
Repository for Molecular Brain Neoplasia Data (REMBRANDT)	NCI, NINDS	NCI	NCI
Research Resource for Complex Physiologic Signals	NIGMS	NIGMS, NIBIB	Beth Israel Deaconess Medical Center
ResearchMatch	NCATS	NCATS	Vanderbilt University
Restoring Insulin Secretion Study (RISE)	NIDDK	NIDDK	Multiple
Retrovirus Epidemiology Study III (REDS III)	NHLBI	NHLBI	RTI International
Retrovirus Resources	NLM	NLM	NLM
RGAP: The Heritable Transcriptome and Alcoholism	NIAAA	NIAAA	University of Colorado, Denver
RxImage API: Image Dataset of Prescription Pills	NLM	NLM	NLM
RxNav	NLM	NLM	NLM
RxNorm	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Salivary Gland Molecular Anatomy Project	NIDCR	NIDCR	NIDCR
Salivary Gland Tumor Biorepository	NIDCR	NIDCR	MD Anderson Cancer Center
Salivary Proteome Wiki Project	NIDCR, CIT	NIDCR, CIT	NIDCR, NIH
Sample Collection Registry for Quality Control of Biological and Environmental Specimens and Assay Development and Testing	NIEHS	NIEHS/NIHCC	NIEHS
Science of Behavior Change Measures Repository	NIA	OD/OSC (Common Fund)	Columbia University Health Sciences
Sea Urchin Genome Database (SpBase)	NICHD	NICHD	California Institute of Technology
Search for Diabetes in Youth Study (SEARCH)	NIDDK, CDC	NIDDK, CDC	Multiple
SEER-Medicare Data	NCI	NCI	NCI
SEER-Medicare Health Outcomes Survey Linked Database	NCI	NCI	NCI
Selenium and Vitamin E Cancer Prevention Trial (SELECT) Biorepository	NCI	NCI	Southwest Cooperative Oncology Group (SWOG)
Semantic LAMHDI: Linking Diseases to Model Organism Resources	OD/ORIP	OD/ORIP	Oregon Health & Science University
SenseLab: Integration of Multidisciplinary Sensory Data	NIDCD	NIDCD, NINDS	Yale University
Sequence Read Archive (SRA)	NLM	NLM	NLM
Severe Chronic Neutropenia International Registry	NIAID	NIAID	University of Washington
SFHERE (Social and Family History - Extraction, Representation, and Evaluation) Digital Library	NLM	NLM	Brown University, University of Minnesota, and University of Vermont
SHARE Israel	NIA	NIA	
Shwachman-Diamond Syndrome International Registry and Repository	NIAID	NIAID, NICHD	Fred Hutchinson Cancer Research Center

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Sign Language Acquisition, Annotation, Archiving and Sharing Platform	NIDCD	NIDCD	Haskins Laboratories, Inc.
Sjögren's International Collaborative Clinical Alliance (SICCA)	NIDCR	NIDCR	University of California, San Francisco
Small Area Estimates for Cancer Risk Factors & Screening Behaviors	NCI	NCI	NCI
SOLAR-Eclipse Computational Tools for Imaging Genetics	NIBIB	NIBIB	University of Maryland
Spin Trap Database	NIEHS	NIEHS	NIEHS
State Cancer Profiles	NCI	NCI, CDC	NCI
Stories of Our Men: American Indian/Alaska Native Colorectal Health	NLM	NLM	Mayo Clinic Rochester
StRAP tool	NCI	NCI	
Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN) Data Coordinating Center	NINDS	NHLBI, NINDS	Medical University of South Carolina
Surveillance, Epidemiology and End Results (SEER)	NCI	NCI	NCI
Survey of Health, Ageing, and Retirement in Europe	NIA	NIA	Munich Center for the Economics of Aging
Swedish Adoption/Twin Study of Aging	NIA	NIA	Karolinska Institutet
Systematic Data Curation and Integration to Link Models of Human Disease	OD/ORIP	OD/ORIP	Princeton University
Taxonomy Database	NLM	NLM	NLM
Technical, Relational, & Conditional Process Models of MI Efficacy: Meta-Analysis	NIAAA	NIAAA	Brown University
Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS)	NIDDK	NIDDK	Multiple
The AnVIL Data Ecosystem	NHGRI	NHGRI	Broad Institute

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
The Automatic Context Measurement Tool: Bringing Environmental Data to Non-specialists	NLM	NLM	University of Washington
The Biological Magnetic Resonance Data Bank (BMRB)	NIGMS	NIGMS	University of Wisconsin
The Brain Tumor Patient-Derived Xenograft National Resource	NINDS	NINDS	Mayo Clinic Rochester
The Cancer Imaging Archive	NCI	NCI	NCI
The Chernobyl Tissue Bank	NCI	NCI	Imperial College
The Disease Ontology	NHGRI	NHGRI	University of Maryland, Baltimore
The EcoCyc Model Organism Database for Escherichia coli	NIGMS	NIGMS	SRI International
The Environmental Determinants of Diabetes in the Young (TEDDY)	NIDDK	NIDDK	Multiple
The Hippocampome Open Source Portal	NINDS	NINDS	George Mason University
The Home Evaluation, Assessment, Rating and Training of Gait (HEART-Gait) System for Monitoring Toe-Walking Severity in Children with Cerebral Palsy	NLM	NLM	Veristride, Inc.
The International Epilepsy Electrophysiology Database (IEEG.ORG)	NINDS	NINDS	University of Pennsylvania
The LA PRISMS Center: The Biomedical REAl-Time Health Evaluation (BREATHE) Platform	NIBIB	NIBIB	UCLA
The Mass Spectrometry Interactive Virtual Environment (MassIVE)	NIGMS	NIGMS	University of California, San Diego
The MetaCyc & BioCyc Pathway/Genome Databases	NIGMS	NIGMS	SRI International
The National Longitudinal Study of Adolescent to Adult Health	NICHD	NICHD	The University of North Carolina at Chapel Hill
The NCI Funded Research Portfolio (NFRP)	NCI	NCI	NCI
The Pediatric Proton Consortium Registry	NCI	NCI	Massachusetts General Hospital

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
The Pregnancy Risk Assessment Monitoring System (Addition of Disability Questions)	NICHD	NICHD, CDC	CDC
The Terabase Search Engine	NHGRI	NHGRI	Johns Hopkins
The United States Immunodeficiency Network (USIDNET)	NIAID	NIAID	Immune Deficiency Foundation
Tobacco Use Supplement to the Current Population Survey	NCI	NCI	U.S. Census Bureau
ToxFx	NIEHS/NTP	NIEHS/NTP	NIEHS/NTP
Toxics Release Inventory (TRI)	NLM	NLM	EPA
TOXLINE (Toxicology Literature Online)	NLM	NLM	NLM
TOXMAP (Environmental Health Maps)	NLM	NLM	NLM
TOXNET (Toxicology Data Network)	NLM	NLM	NLM
Trace Assembly Archive	NLM	NLM	NLM
Training & Tools for Informationists to Facilitate Sharing of Next Generation Sequencing Data	NLM	NLM	Johns Hopkins University
Transcriptome Resources	NIAID	NIAID	NIAID
Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Information Commons	NINDS	NINDS	University of California, San Francisco
Transplant Cancer Match Study	NCI	NCI	NCI, HRSA
Transporter Classification Database (TCDB)	NIGMS	NIGMS, NIAID	University of California, San Diego
Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study, Follow-up, and Genetics Study	NIDDK	NIDDK	Multiple (The George Washington University, DCC)
Tuberculosis Portals	NIAID	NIAID	NIAID
Turning the Pages – Rare Historic Works	NLM	NLM	NLM
UMLS (Unified Medical Language System)	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Unifying Templates; Ontologies and Tools to Achieve Effective Annotation of Bioassay Protocols	NLM	NLM	University of Miami School of Medicine
UniGene	NLM	NLM	NLM
UniProt Protein Sequence and Function Knowledgebase	NHGRI	NHGRI, NIGMS, NIA, NIMHD, NEI, NIDDK, NHLBI	European Molecular Biology Laboratory
United States Renal Data System (USRDS)	NIDDK	NIDDK	NIDDK
United States Renal Data System Coordinating Center	NLM	NLM	University of Michigan at Ann Arbor
University of California, Santa Cruz Genome Browser	NHGRI	NHGRI, OD	University of California Santa Cruz
URBAN ARCH Consortium	NIAAA	NIAAA	Boston Medical Center
Value Set Authority Center (VSAC)	NLM	NLM	NLM
Vasculitis Clinical Research Consortium (VCRC)	NIAMS	NIAMS	University of Pennsylvania
VectorBase (Invertebrate Vectors of Human Pathogens)	NIAID	NIAID	University of Notre Dame
Vietnam Era Twin Study of Aging	NIA	NIA	Boston University
Viral Genomes	NLM	NLM	NLM
Virus Pathogen Resource (ViPR)	NIAID	NIAID	Northrup Grummon Health IT, J. Craig Venter Institute
Visible Human Project	NLM	NLM	NLM
Vitamin D and Type 2 Diabetes Study	NIDDK	NIDDK, OD	Multiple (Tufts Medical Center, DCC)
WHO's Study on Global Aging and Adult Health	NIA	NIA	World Health Organization
Wireless Information System for Emergency Responders (WISER)	NLM	NLM	NLM
Wisconsin Longitudinal Study	NIA	NIA	University of Wisconsin

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Wisconsin Registry for Alzheimer's Prevention: Biomarkers of Preclinical AD	NIA	NIA	University of Wisconsin, Madison
Women's Interagency HIV Study (WIHS) Public Dataset	NIAID	NIAID, NICHD, NCI, NIDA, NIMH, NHLBI	Johns Hopkins University; Hektoen Institute of Medicine; University of California, San Francisco; Einstein University/Montefiore Medical Center; State University of New York—Brooklyn; Georgetown University; The University of Alabama at Birmingham; University of Miami; Emory University, The University of North Carolina
World Report	FIC	FIC, NIH	All NIH ICs, for other participating institutions see: https://worldreport.nih.gov/about.cfm
WormGUIDES (Global Understanding in Dynamic Embryonic Systems)	OD/ORIP	OD/ORIP	Yale University
Xenbase: A Xenopus Model Organism Database	NICHD	NICHD	Cincinnati Children's Hospital Medical Center
XNAT Open Source Informatics for Imaging Research	NIBIB	NIBIB	Washington University
ZFIN: The Zebrafish Model Organism Database	NHGRI	NHGRI	University of Oregon

Appendix H:
Actions Undertaken to Carry Out Scientific Frameworks on Recalcitrant Cancer

In response to the *Recalcitrant Cancer Research Act of 2012* NCI developed scientific frameworks for two recalcitrant cancers:

- Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)[1]
- Scientific Framework for Small Cell Lung Cancer (SCLC)[2]

This appendix includes an assessment of the progress made in improving outcomes for individuals diagnosed with PDAC and SCLC; an update on activities pertaining to these cancers, including actions undertaken to carry out the two scientific frameworks; and information on research grants awarded by NIH for research relating to these cancers.

Assessment of Progress

In the U.S., PDAC is the third leading cause of cancer-related death in both men and women, with a five-year relative survival rate of 9.3 percent. In part because pancreatic cancer is usually diagnosed at an advanced stage, the survival rate is extremely low compared with that of many other cancer types. The incidence of pancreatic cancer is increasing in the Western World. The Surveillance, Epidemiology, and End Results Program (SEER) found that between 1973 and 2014 the age-standardized incidence rates of pancreatic cancer increased by 1.03 percent per year, predicting a rise in PDAC to being the second most common cause of cancer-related deaths in the U.S. by 2030.[3,4]

SCLC has a similarly low five-year relative survival rate of less than 7 percent. As noted in the *Scientific Framework for SCLC*, the disease is highly associated with cigarette smoking, and the decrease in cigarette smoking in the U.S. population is reflected in the decrease in the incidence of SCLC over the past 30 years, with continued decreases expected.

Although the framework for the triennial reports indicates a request for relative survival rates, mortality rates are preferred. Relative survival rates may be misleading for at least two reasons. First, lead-time bias is possible, in which a diagnosis earlier in the disease but without an improved clinical response is recorded

[1] http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf.
[2] http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLC%20Congressional%20Response.pdf.
[3] Siegel RL, et al. *CA Cancer J Clin* 2018;68(1):7-30. PMID: 29313949.
[4] Rahib L., et al. *Cancer Res* 2014;74:2913-2921. PMID: 24840647.

incorrectly as improvement. Second, relative survival rates focus only on those patients who develop the disease. This consideration is important for SCLC, where tobacco consumption is an important risk factor, and probably to some degree for PDAC, as well. For example, if decreased smoking led to a 50 percent reduction in the incidence and mortality for SCLC, this reduction should be seen as progress, even with no change in the relative survival rate.

NCI calculates mortality rates by using population-level data collected through its SEER program. In assessing progress made toward improving mortality rates, the time necessary to collect and analyze the data is a critical factor. One problem inherent in estimating mortality rates is that patient cohorts must be followed for many years after diagnosis to calculate accurate rates. The relative mortality rates for patients diagnosed with PDAC and SCLC in recent years will be based on data still being collected.

As described in detail in the *Scientific Framework for PDAC* and the *Scientific Framework for SCLC*, NCI is supporting critical research that aims to improve outcomes in each of these disease areas. Scientific progress is being made toward better understanding both PDAC and SCLC, and NCI is continuing to prioritize research on these diseases in an effort to translate this progress into improved prevention, diagnosis, treatment, and quality of life for patients.

Update on Pancreatic Ductal Adenocarcinoma (PDAC) Activities, FY 2016–2018

NCI convened a panel of experts for a workshop to develop the scientific framework for PDAC in October 2012. The workshop report, *Pancreatic Cancer: Scanning the Horizons for Focused Interventions*,[5] was developed over the following year and was presented to and accepted by the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) in March 2013.

The *Scientific Framework for Pancreatic Ductal Adenocarcinoma*, submitted to Congress in February 2014, provides the background, rationale, and implementation plans for four initiatives proposed to expand PDAC research. An *Interim Progress Report*[6] by the Progress in PDAC Research Working Group was provided to CTAC in November 2015. The Progress in PDAC Research Working Group was reconvened in September 2018. A panel of experts met via multiple webinars to discuss current pancreatic cancer research in relation to each of the 2014 scientific initiatives. The overall impression was that the initiatives in the scientific framework were still relevant. These initiatives, along with corresponding NCI activities, are summarized below.

Understand the Biological and Clinical Relationship Between PDAC and Recent-Onset Diabetes Mellitus

Understanding the clinical and biological characteristics of new onset diabetes patients who subsequently develop or have undiagnosed PDAC is important for defining risk factors for screening and early diagnosis efforts.

[5] https://deainfo.nci.nih.gov/advisory/ctac/archive/0313/PCwgReport.pdf.
[6] http://deainfo.nci.nih.gov/advisory/ctac/1115/8-PDACwgReport.pdf.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with co-funding from NCI, supports the Consortium for the Study of Chronic Pancreatitis Diabetes and Pancreatic Cancer (CPDPC) to pursue clinical research on pancreatic diseases, including pancreatic cancer.[7] The Consortium has developed four large studies: PROCEED (Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies) to study chronic pancreatitis; INSPPIRE (InterNational Study group of Pediatric Pancreatitis: In search for a cuRE) to study pediatric pancreatitis; DETECT (evaluation of a mixed-meal test for Diagnosis and characterization of pancrEaTogEniC diabeTes secondary to pancreatic cancer and chronic pancreatitis) to distinguish Type 3c diabetes from Type 2 diabetes; and NoD (New-onset Diabetes) to study pancreatic cancer in patients with newly diagnosed diabetes.

Develop New Molecular and Imaging Biomarkers for Early Detection of PDAC and Its Precursors

The NCI Pancreatic Cancer Detection Consortium[8] aims to develop and test new molecular and imaging biomarkers to improve the detection of early-stage PDAC, and to identify individuals at high risk who may be candidates for early intervention.

The NCI Early Detection Research Network (EDRN)[9] supports research to validate biomarkers in blood, cystic fluids, and tissues that may be useful in the early detection and treatment of PDAC. A major consideration is the ability to identify those who are at high risk for developing PDAC from among the many patients who are found to have pancreatic cysts. NCI also supports three pancreatic cancer Specialized Programs of Research Excellence (SPOREs)[10] and one gastrointestinal (GI) cancer SPORE that is predominantly focused on pancreatic cancer. As part of these research initiatives, an NCI-supported translational research team developed a new noninvasive blood test to detect eight common cancer types, including pancreatic cancer.[11]

Implement New Immunotherapy Approaches Based on a Deeper Understanding of How PDAC Interacts with Its Potentially Immunosuppressive Microenvironment

The Cancer Immunotherapy Trials Network has prioritized pancreatic cancer immunotherapy studies. Recent data indicate that promotion of T-cell–dependent antitumor immunity can produce tumor regressions in patients with metastatic pancreatic cancer.

The Pancreatic Cancer Microenvironment Network, a Cancer Moonshot project, is making advances in immunotherapy options by studying of the interaction between pancreatic tumors and their microenvironment.[12] Multidisciplinary NCI-supported research teams are investigating the role of the immune system in PDAC development and working to develop more effective treatments. These

[7] https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection/pcdc-resources-and.
[8] https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection/about-pcdc.
[9] https://edrn.nci.nih.gov/.
[10] https://trp.cancer.gov/spores/pancreatic.htm.
[11] Cohen J., et al. *Science* 2018;359: 926-930. PMID: 29348365.
[12] https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/adult-immunotherapy-network.

teams are focusing on understanding the interaction between tumors and the microenvironment to develop approaches to enhance the immune response against pancreatic cancers. New evidence suggests it is possible to reprogram the tumor microenvironment to make PDAC more amenable to immunotherapy.

Develop New Treatment Strategies That Interfere with RAS Oncogene-Dependent Signaling Pathways.

The NCI RAS Initiative[13] at the Frederick National Laboratory for Cancer Research seeks to better understand the role of RAS mutations (common in PDAC) in the development of cancer and to explore new treatments to neutralize mutant RAS proteins. The major goals are to discover small molecules that bind to RAS directly or disrupt RAS/effector interactions and to molecularly describe the RAS/RAF signaling complexes in the membranes. The NCI RAS Initiative has organized multiple events to discuss how the latest scientific and technological breakthroughs can be applied to discover vulnerabilities in RAS-driven cancers.

The *RAS Initiative Symposium* was held in December of 2015 (at the start of FY 2016) and brought experts together to discuss a broad cross-section of RAS-related research in areas ranging from structural biology to signaling pathways to novel therapeutic approaches.

Other meetings include the *RAS Immunotherapy Workshop* that was held in November 2015, the *Synthetic Lethality Network Principal Investigators Meeting* held in December 2015, the *Fully Processed KRAS Protein Purification Workshop* held in May 2016, and the *RAS Structure and Dynamics in Membranes Workshop* held in October 2016.

Other Research

In addition to supporting research in those areas emphasized in the *2014 Scientific Framework for PDAC*, NCI continues to support research in other areas that may benefit PDAC patients. For example, 430 pancreatic cancer patients were enrolled in the NCI Molecular Analysis for Therapy Choice (NCI-MATCH), a precision medicine trial that is expected to advance research on all types of cancer, including pancreatic cancer.[14] NCI-supported investigators also are pursuing a cancer vaccine that prevents PDAC by targeting an abnormal form of a protein. Additionally, NCI continues to support investigator-initiated research projects focusing on pancreatic cancer. The table at the end of this appendix contains a full list of all NCI-supported PDAC research projects for FY 2016–2018.

[13] https://www.cancer.gov/research/key-initiatives/ras.
[14] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.

Update on Small Cell Lung Cancer (SCLC) Activities, FY 2016–2018

The Scientific Framework for Small Cell Lung Cancer,[15] submitted to Congress in June 2014, provides the background, rationale, and implementation plans for five initiatives proposed to expand SCLC research. These initiatives are summarized below:

- *Build Better Research Tools for the Study of SCLC.* Build better research tools for the study of SCLC by (1) optimizing the collection of tumor tissue specimens representing distinct phases of SCLC (from initial diagnosis to disease recurrence following radio-chemotherapy) and (2) developing new tumor models (e.g., cell lines, patient-derived xenografts, genetically engineered mouse models) that reflect the phases of SCLC found in the clinic.
- *Conduct Comprehensive Genomic Profiling of SCLC.* Expand comprehensive genomic profiling studies of clinically annotated SCLC specimens to improve the basic understanding of the frequency, distribution, and range of molecular abnormalities that exist both at diagnosis and following therapeutic relapse.
- *Develop New Diagnostic Approaches for SCLC.* Investigate new diagnostic approaches for populations at high risk of developing SCLC.
- *Develop New Therapeutics for SCLC.* Focus therapeutic development efforts on specific molecular vulnerabilities of SCLC (tumor suppressor genes, unique genetic drivers and their pathways, neuronal characteristics, and immunotherapy).
- *Understand the Mechanisms Underlying Both the High Rate of Initial Response and Rapid Emergence of Drug and Radiation Resistance.* Examine the mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following completion of treatment.

In December 2015, NCI issued a series of funding opportunity announcements with special review to support and establish the SCLC Consortium, which is intended to address each of the five initiatives from the scientific framework:

- PAR-16-049: Small-Cell Lung Cancer (SCLC) Consortium: Therapeutic Development and Mechanisms of Resistance (U01)[16]
- PAR-16-050: Small Cell Lung Cancer (SCLC) Consortium: Coordinating Center (U24)[17]
- PAR-16-051: Small-Cell Lung Cancer (SCLC) Consortium: Innovative Approaches to the Prevention and Early Detection of Small Cell Lung Cancer (U01)[18]

Investigators in the SCLC Consortium meet annually to share scientific progress and opportunities for collaboration. The first meeting of SCLC Consortium investigators was held in March 2018.

[15] http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLC%20Congressional%20Response.pdf.
[16] https://grants.nih.gov/grants/guide/pa-files/par-16-049.html.
[17] https://grants.nih.gov/grants/guide/pa-files/par-16-050.html.
[18] https://grants.nih.gov/grants/guide/pa-files/par-16-051.html.

In January 2016, the Progress in SCLC Research Working Group was convened to advise NCI on the progress of the research initiatives outlined in the scientific framework for SCLC. The Working Group's assessment was that NCI implementation activities were on target for each of the five initiatives, but it was too early to assess scientific progress. The interim progress report[19] of the Working Group was presented to and accepted by CTAC in July 2016.

NCI participated in a workshop with the International Association for the Study of Lung Cancer (IASLC) to continue to engage the research community in advancing the research agenda described in the scientific framework and to identify new research opportunities. Like the inaugural workshop in April 2015, the April 2017 IASLC Small Cell Lung Cancer Workshop was attended by many investigators from the international research community. NCI scientific and program staff took part in the meeting and helped in its organization.

The NCI Thoracic Malignancy Steering Committee made the rapid testing of new agents and strategies for the treatment of SCLC one of its strategic priorities in 2015.

Since then, the NCI National Clinical Trials Network has opened NCT03382561,[20] a trial studying cisplatin/carboplatin and etoposide with or without nivolumab to treat patients with extensive stage SCLC; NCT03811002,[21] a trial studying chemoradiation with or without atezolizumab to treat patients with limited stage SCLC; and NCT02635009,[22] a trial studying whole-brain radiation therapy with or without hippocampal avoidance to treat patients with limited stage or extensive stage SCLC.

[19] https://deainfo.nci.nih.gov/advisory/ctac/0716/4-SCLprogressReport_Jul%202016.pdf.
[20] https://clinicaltrials.gov/ct2/show/NCT03382561.
[21] https://clinicaltrials.gov/ct2/show/NCT03811002.
[22] https://clinicaltrials.gov/ct2/show/NCT02635009.

FY 2016, 2017, and 2018 NIH Projects Related to Pancreatic Ductal Adenocarcinoma (PDAC)

Project Number	Title	Principal investigator(s)	Institution
DP1CA228041	Enhancer RNA Therapy	Shiekhattar, Ramin	University of Miami School of Medicine
DP2CA216364	Tracking Tumor Evolution through *In Vivo* Organelle Profiling	Perera, Rushika Miriam	University of California, San Francisco
DP2CA228042	Dissecting Tumor Metabolic Heterogeneity *In Vivo*	Birsoy, Kivanc	The Rockefeller University
DP5OD26427	Immune Activating CAR-Modified Antigen Presenting Cells	Deselm, Carl	Washington University
F30CA180601	The Role of p120ctn in Pancreatic Ductal Morphogenesis and Adenocarcinoma	Bakir, Basil	University of Pennsylvania
F30CA183474	Investigating Branched Chain Amino Acid Metabolism in Pancreatic Cancer	Mayers, Jared R	Harvard Medical School
F30CA189793	Design and Development of a Small Molecule-controlled Activator of RAS	Rose, John Christopher	University of Washington
F30CA192819	A Differentiation-Based Mechanism Limiting Pancreatic Tumor Initiation	Krah, Nathan Michael	The University of Utah
F30CA196040	Structural Basis of Chemokine Receptor Signaling in Tumor Progression	Kleist, Andrew B	Medical College of Wisconsin
F30CA196087	TSPO-PET to Image Pancreatic Cancer and High-Risk Precursor Lesions	Watchmaker, Jennifer M	Vanderbilt University
F30CA196106	A Role for Macrophage Phenotype in Regulating Metastasis in Pancreatic Carcinoma	Lee, Jae	University of Pennsylvania
F30CA196124	Pro- and Anti-phagocytic Signals on Pancreatic Cancer Regulate Tumor Macrophages	Liu, Mingen	University of Pennsylvania
F30CA200240	Role of Nix in Pancreatic Ductal Adenocarcinoma	Alagesan, Brinda	State University New York at Stony Brook

Project Number	Title	Principal investigator(s)	Institution
F30CA200301	Mechanistic and Informatics Based Analysis of STAT1 Actions in Pancreatic Cancer	Craven, Kelly Eileen	Indiana University, Purdue University at Indianapolis
F30CA203238	Mechanisms of Escape from TGFβ Tumor Suppression in the Pancreas	Huang, Yun-Han	Weill Medical College of Cornell University
F30CA206240	Mechanisms of Pancreatic Carcinogenesis	He, Ping	State University New York at Stony Brook
F30CA210587	Mechanisms Behind CCL21/CCR7-Mediated Pancreatic Cancer Progression	Moussouras, Natasha A	Medical College of Wisconsin
F30CA213745	The Role of Leukocytes in the Hypothalamus in Cancer Cachexia	Burfeind, Kevin Glenn	Oregon Health & Sciences University
F30CA213883	Identifying Novel Effectors of Oncogenic Kras in Pancreatic Cells via Proximity Labelling	Cheng, Derek Kingman	State University New York at Stony Brook
F30CA213916	FOLFOX-Induced Kinome Reprogramming in Pancreatic Cancer Tumor Xenografts	Lipner, Matthew	The University of North Carolina at Chapel Hill
F30CA216998	The Role of ITIH5 in Suppressing Pancreatic Cancer Metastasis	Young, Eric	University of Kansas Medical Center
F30CA220680	Physiological Role of Dynamin-Related Protein 1 in Pancreatic Ductal Adenocarcinoma	Nagdas, Sarbajeet	University of Virginia
F30CA220843	Development of a Novel Antibody Drug Conjugate for the Treatment of Pancreatic Cancer	Gromisch, Christopher Marr	Boston University Medical Campus
F30CA221175	LINE-1 Genotoxicity and Cytotoxicity and Its Relevance to Cancer	Ardeljan, Daniel	Johns Hopkins University
F30CA224970	Investigating the Role of C1-INH in Pancreatic Ductal Adenocarcinoma Progression	Yuan, Salina	University of Pennsylvania
F30CA225117	CXCR3 in Pancreatic Cancer Progression and Metastasis	Cannon, Andrew C	University of Nebraska Medical Center

Project Number	Title	Principal investigator(s)	Institution
F30HL117546	Microparticle Docking in Pancreatic Cancer Induced VTE	Geddings, Julia E	The University of North Carolina at Chapel Hill
F31CA177163	Elucidating the Role and Regulation of Epithelial Plasticity in Metastasis	Aiello, Nicole	University of Pennsylvania
F31CA180628	Defining the Role and Mechanism of Pak1 in Supporting Pancreatic Cancer	Baker, Nicole Marie	The University of North Carolina at Chapel Hill
F31CA180693	Targeting K-Ras Effector Signaling for Pancreatic Cancer Treatment	Hayes, Tikvah K	The University of North Carolina at Chapel Hill
F31CA180738	Genetic and Pharmacological Manipulation of System XC in Pancreatic Cancer	Badgley, Michael Alexander	Columbia University Health Sciences
F31CA183493	Tumor Expressed B7x Accelerates Disease and Is a Novel Target for Immunotherapy	Ohaegbulam, Kim C	Albert Einstein College of Medicine
F31CA186513	Intact Protein as a Cancer Fuel Source	Nofal, Michel	Princeton University
F31CA192767	Inhibiting UAP1/2 as a Novel Strategy for Regulating Carbohydrate Metabolic Flux	Saeui, Christopher	Johns Hopkins University
F31CA192829	Defining the Role of ERK1 and ERK2 in Pancreatic Cancer	Ryan, Meagan B	The University of North Carolina at Chapel Hill
F31CA192890	Determining the Kinetics and Mechanism of Pancreatic Tumor Regression Following Genetic Deletion of PI3K p110a	Chapelliquen, Stephanie Rose	State University New York at Stony Brook
F31CA196329	Tumor-Associated Physiological Changes Arising from Ras-Induced Mitochondrial Fission	Nascimento, Aldo	University of Virginia
F31CA203563	Investigating the Role of Novel Drug Target TBK1 in Pancreatic Cancer Pathogenesis	Brannon, Arthur Lee	University of Michigan at Ann Arbor
F31CA206233	High-Throughput Generation of Pancreatic Organoids with Controlled Stromal Milieus Using Microraft-Based Cell Sorting	Disalvo, Matthew	The University of North Carolina at Chapel Hill

Project Number	Title	Principal investigator(s)	Institution
F31CA206416	Stem Cell Signals in Pancreatic Adenocarcinoma Metastasis and Therapy Resistance	Lytle, Nikki Katherine	University of California, San Diego
F31CA210627	Functional Interrogation of Kdm6a-Dependent Tumor Suppression During Pancreatic Cancer	Winters, Ian Paul	Stanford University
F31CA210631	Elucidating the Role of Fasting in GI Radioprotection: Applications in Pre-Clinical Pancreatic Cancer Model	De La Cruz Bonilla, Marimar	The University of Texas MD Anderson Can Center
F31CA213731	Pathophysiological Role and Therapeutic Potential of MicroRNA-29 in Pancreatic Cancer Autophagy	Kwon, Jason	Indiana University-Purdue University at Indianapolis
F31CA217070	Role of the Hexosamine Biosynthesis Pathway in Pancreatic Cancer	Campbell, Sydney	University of Pennsylvania
F31CA220750	At the Nexus of Redox and Signaling Pathways: Regulation of NAD+ Kinase	Schild, Tanya	Weill Medical College of Cornell University
F31CA220937	The Novel Role of REST in the Development of Pancreatic Ductal Adenocarcinoma	Bray, Julie	University of Florida
F31CA220966	Determining the Role of Discoidin Domain Receptor 2 in the Pathogenesis of Pancreatic Ductal Adenocarcinoma	Ruggeri, Jeanine	University of Michigan at Ann Arbor
F31CA220970	Image-guided, Sonoporation-Enhanced Immunotherapy for Pancreatic Cancer Treatment	Fix, Samantha Marie	The University of North Carolina at Chapel Hill
F31CA221066	Examining the Heterogeneity of Fibroblasts in the Pancreatic Microenvironment	Garcia, Paloma Elizabeth	University of Michigan at Ann Arbor
F31CA224792	Identifying Molecular Drivers of Tumor Heterogeneity in Pancreatic Cancer	Adams, Christina R	University of California, San Francisco
F31CA224942	Chloroquine Drug Delivery System for Sensitization of Pancreatic Cancer to Improve Oxaliplatin Efficacy	Sleightholm, Richard L	University of Nebraska Medical Center

Project Number	Title	Principal investigator(s)	Institution
F31CA228223	A Combined Single Cell Gene Expression and Enzyme Activity Assay to Study Chemotherapy Resistance in Pancreatic Ductal Adenocarcinoma	Petersen, Brae	The University of North Carolina at Chapel Hill
F31CA236332	Novel Molecular Mechanisms Dictating Pancreatic Cancer Metastasis in Tip30-Deficient Kras-Mutant Mice	Imasuen-Williams, Imade	Indiana University-Purdue University at Indianapolis
F31EB22414	In-vivo Characterization of Pancreatic Field Carcinogenesis Using Spatially Resolved Reflectance Measurements via a Fiber Optic Probe	Eshein, Adam	Northwestern University
F31EY26786	Determining the Role of 3-D Nuclear Architecture in Stochastic Gene Expression	Viets, Kayla Chelsea	Johns Hopkins University
F31HG8912	Computational Modeling of Heterogeneous Gene Expression in Single Cells	Welch, Joshua	The University of North Carolina at Chapel Hill
F32CA177072	Mechanisms of tumor suppression by epigenetic regulators in pancreatic cancer	Livshits, Geulah Yevgeniya	Sloan-Kettering Instititute
F32CA180452	Developing an Anti-sialyl-Lewisa Diabody for ImmunoPET Imaging of Pancreas Cancer	Houghton, Jacob	Sloan-Kettering Institute
F32CA180717	The Characterization of the New Tumor Suppressor USP9X in Pancreatic Cancer	Hwang, Chang-Il	Cold Spring Harbor Laboratory
F32CA189633	Targeted Delivery of Theranostic Nanoparticles Carrying Immune Modulators	Bozeman, Erica	Emory University
F32CA192769	MYC is a Critical Downstream Effector in KRAS-Driven Pancreatic Cancer	Allen-Petersen, Brittany	Oregon Health & Science University
F32CA192786	Novel Combination Therapeutic Strategies to Ablate Resistance to Hsp90 Inhibitors	Koren, John	Sloan-Kettering Institute

Project Number	Title	Principal investigator(s)	Institution
F32CA192904	Finding Novel Pancreatic Cancer Oncogenes Using an Innovative 3-D Culture System	Baker, Lindsey A	Cold Spring Harbor Laboratory
F32CA196120	A Cell-based Liquid Biopsy Approach for Early Pancreatic Cancer Detection	Bhagwat, Neha	University of Pennsylvania
F32CA200024	Munc13-4 Regulates Ca2+-Stimulated Exosome Release During EMT	Messenger, Scott W	University of Wisconsin–Madison
F32CA200078	Chemical Genetic Investigation of Metastatic Seeding in Pancreatic Ductal Adenocarcinoma Using Novel Multiplexed *In Vivo* Screening	Schulze, Christopher James	Stanford University
F32CA200278	Novel BPTES Analogs for the Treatment of Pancreatic Cancer	Zimmermann, Sarah	Johns Hopkins University
F32CA200313	K-Ras Mutant-Specific Vulnerabilities for Novel Pancreatic Cancer Therapies	Hobbs, Guy Aaron	The University of North Carolina at Chapel Hill
F32CA206234	Exploring BCL-XL Addiction in Pancreatic Ductal Adenocarcinoma	Soderquist, Ryan	Duke University
F32CA206330	Novel Pancreatic Cancer T Cell Immunotherapy	Woodham, Andrew Wallace	Whitehead Institute for Biomedical Research
F32CA210387	The Role of Prrx1 in Acinar-ductal Metaplasia During Pancreatic Tumorigenesis	Collins, Meredith A	University of Pennsylvania
F32CA210396	Development of 18F-Based Pretargeted PET Imaging Strategies for the PET Imaging of Cancer	Meyer, Jan-Philip	Sloan-Kettering Institute
F32CA210421	Understanding Cell intrinsic and Context Dependent Metabolic Adaptations of Cancer Cell	Danai, Laura Victoria	Massachusetts Institute of Technology
F32CA210568	Targeting Cytokines to the Tumor Microenvironment Using a High Affinity Single Domain Antibody to PD-L1	Dougan, Michael Lawrence	Massachusetts General Hospital
F32CA213764	The Role of Neuroendocrine	Morrison Joly, Meghan Melinda	Oregon Health & Science University

Project Number	Title	Principal investigator(s)	Institution
	Transdifferentiation of Pancreatic Cancer Cells on Tumor Progression and Chemoresistance.		
F32CA213795	Targeting Hyaluronan in the Tumor Microenvironment to Improve DNA Vaccine Immunotherapy	Duperret, Elizabeth Kennedy	The Wistar Institute
F32CA213810	Understanding Metabolic Pathways That Support Redox Homeostasis in Cancer	Muir, Alexander	Massachusetts Institute of Technology
F32CA217033	Epigenetic Therapy for Pancreatic Cancer	Liang, Gaoyang	Salk Institute for Biological Studies
F32CA217455	Impact of Volume-Based Regionalization on Access to Care in Patients Undergoing Pancreatectomy	Fong, Zhi Ven	Massachusetts General Hospital
F32CA221005	Targeting CDK4/6 for Pancreatic Cancer Treatment	Goodwin, Craig	The University of North Carolina at Chapel Hill
F32CA221094	The Role of p120ctn in PDAC Epithelial-to-Mesenchymal Transition and Metastasis	Pitarresi, Jason R	University of Pennsylvania
F32CA221114	Examination of Ceramide Signaling in the Crosstalk Between Pancreatic Cancer Cells and the Tumor Microenvironment	Hendley, Audrey Marie	University of California, San Francisco
F32CA225040	Proteomic and Genomic Characterizations of FOXP1 in Pancreatic Cancer	Bowman, Brittany M	The University of North Carolina at Chapel Hill
F32CA228328	Targeting Epithelial-Immune Cell Crosstalk to Improve Therapy in Pancreatic Cancer	Halbrook, Christopher J	University of Michigan at Ann Arbor
F32CA232529	Defining the Contributions of WT RAS in RAS-Mutant Lung Cancer	Stalnecker, Clint A	The University of North Carolina at Chapel Hill
F32CA232543	The Novel PRMT5-Substrate Adaptor Interface Provides a Therapeutic Target in MTAP Null Tumors	Mulvaney, Kathleen	Broad Institute, Inc.

Project Number	Title	Principal investigator(s)	Institution
F32EB18715	Contrast-Enhanced Intravascular Ultrasound Imaging of Vascular Invasion	Lindsey, Brooks D	The University of North Carolina at Chapel Hill
F99CA223029	Class III PI3K as an Autophagy Reactivation Switch in Malignant Transformation	Young, Lindsey N	University of California, Berkeley
F99CA223043	Defining the Barriers to Immune Surveillance in Solid Tumors	Hegde, Samarth	Washington University
F99CA234962	Pancreatic Cancer Stem Cells: PD2-Mediated Novel Mechanistic Link and Metabolomic Alterations	Karmakar, Saswati	University of Nebraska Medical Center
K01DK98285	Resolving the Role of Nicotine-Mediated Phosphorylation on Pancreatic Fibrosis	Paulo, Joao A	Harvard Medical School
K07CA204201	Video Informed Consent Tools to Improve Care for Patients with Advanced Pancreatic Cancer	Enzinger, Andrea C	Dana–Farber Cancer Institute
K07CA222159	Obesity and Pancreatic Cancer Progression and Survival	Babic, Ana	Dana–Farber Cancer Institute
K08CA172676	Exploration of a Mutant p53 Reactivating Compound	Carpizo, Darren Richard	Rutgers Cancer Institute of New Jersey
K08CA201581	Role of Interleukin-22 and Innate Lymphoid Cells in Pancreas Cancer Initiation and Progression	Frankel, Timothy Louis	University of Michigan at Ann Arbor
K08CA208016	Elucidating KRAS-Specific Vulnerabilities in Pancreatic Cancer	Muzumdar, Mandar Deepak	Dana–Farber Cancer Institute
K08CA218420	Functional Interrogation of Epigenetic Vulnerabilities in KRAS-mutant Pancreatic Cancer	Aguirre, Andrew James	Dana–Farber Cancer Institute
K08CA218690	Defining Diverse Roles of p53 in Pancreatic Cancer	Kim, Michael Paul	The University of Texas MD Anderson Cancer Center
K08CA222611	Arid1a Loss Accelerates Pancreatic Ductal Adenocarcinoma Precursor Formation	Wang, Sam C	UT Southwestern Medical Center

Project Number	Title	Principal investigator(s)	Institution
K08CA234222	Linking Epigenetic Regulation and TGF-β Signaling in Pancreatic Cancer	Shi, Jiaqi	University of Michigan at Ann Arbor
K08DK105326	The Role of NR5A2 in Pancreas Development and Disease	Nissim, Sahar	Brigham and Women's Hospital
K08DK107781	Characterization of the Molecular Determinants of High-Grade Dysplasia in Pancreatic Cancer Precursor Lesions	Wood, Laura Delong	Johns Hopkins University
K08DK109492	The Role of Progenitor Cells in Pancreatic Acinar Renewal and Pre-malignant Progression	Maddipati, Ravikanth	University of Pennsylvania
K22CA175260	PD2/Paf1 and Pancreatic Cancer Stem Cells	Ponnusamy, Moorthy P	University of Nebraska Medical Center
K22CA178309	Parental Exposure to High Fats Diets and Risk of Pancreatic Cancer in the Offspring	De Assis, Sonia	Georgetown University
K22CA181611	Online Monitoring and Image-Guided Treatment of Chemoresistant Micrometastases	Spring, Bryan Quilty	Northeastern University
K22CA226037	Identification of Key Regulators in Pancreatic Cancer Metastasis	Hwang, Chang-Il	University of California, Davis
K99AR71508	The Extracellular Matrix in Muscle Atrophy	Talbert, Erin E	Medical University of South Carolina
K99CA188259	Regulation of Cancer Cell Metabolism and Growth by the Pancreatic Tumor Stroma	Sherman, Mara H	Salk Institute for Biological Studies
K99CA190889	Integrative Analyses to Identify Pancreatic Cancer Susceptibility Genes	Roberts, Nicholas Jason	Johns Hopkins University
K99CA197816	The SMYD3-ERK5 Signaling Module in Pancreatic Cancer	Mazur, Pawel K	Stanford University
K99CA204725	Exploring Glycobiology and Discovering Biomarkers for Pancreatic Cancer	Engle, Dannielle	Cold Spring Harbor Laboratory
K99CA207870	Recombinant Antibodies Containing L-DOPA for	Thyer, Ross T	The University of Texas at Austin

Project Number	Title	Principal investigator(s)	Institution
	Stability, Functionalization and Selection		
K99CA208032	Deciphering the Role of Lin28b in Pancreatic Cancer to Guide Therapeutic Discovery	Kugel, Sita	Massachusetts General Hospital
K99CA218891	Targeting Malic Enzyme 3 as a Synthetic Lethality Target in Pancreatic Cancer	Dey, Prasenjit	The University of Texas MD Anderson Cancer Center
K99CA218892	Uncovering Roles of Polyunsaturated Fatty Acids in Pancreatic Cancer Etiology	Wu, Lang	Vanderbilt University Medical Center
K99CA226342	Altered mRNA Splicing Dependent on Mutant p53 Identifies Novel Therapeutic Vulnerability in Pancreatic Cancer	Escobar Hoyos, Luisa	Sloan-Kettering Institute
K99CA234221	Understanding Metabolic Heterogeneity in Pancreatic Cancer	Lau, Allison N	Massachusetts Institute of Technology
N01CA0	Phase III Trial of Carbon Ion Therapy	Guha, Chandan	Albert Einstein College of Medicine, Inc.
N01CA0	Igf Ot Igf Cancer Prevention by Alpha Enolase Vaccination	Brown, Paul	The University of Texas MD Anderson Cancer Center
N01CA0	Igf::Ot::Igf Phase III Trial of Carbon Ion Therapy	Guha, Chandan	Albert Einstein College of Medicine
N01CA0	Effect of A Multipeptide Kras Vaccine in the Prevention of Pancreatic Cancer Driven by Kras Oncoprotein	You, Ming	Medical College of Wisconsin
N43CA0	Igf::Ot::Igf Targeted Radionuclide Therapy of Pancreatic Cancer	Budde, Raymond Joseph	Houston Pharmaceuticals, Inc.
P01CA117969	Genetics and Biology of Pancreatic Ductal Adenocarcinoma	Depinho, Ronald Anthony	The University of Texas MD Anderson Cancer Center
P01CA120964	Molecular Pathogenesis of the Hamartoma Syndromes	Kwiatkowski, David J	Brigham and Women's Hospital
P01CA13106	Cold Spring Harbor Laboratory Cancer Research Center	Stillman, Bruce W	Cold Spring Harbor Laboratory

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P01CA159992	Magnetic Resonance Imaging-Guided Cancer Interventions	Butts-Pauly, Kim (Contact); Daniel, Bruce L	Stanford University
P01CA163200	Targeting Diet-Induced Promotion of Kras-Initiated Pancreatic Adenocarcinoma	Eibl, Guido Erwin Michael	University of California, Los Angeles
P01CA203657	Defining RAS Isoform-and mutation-specific Roles in Oncogenesis	Der, Channing J	The University of North Carolina at Chapel Hill
P01CA210944	Radiation and Checkpoint Blockade for Cancer Immune Therapy	Vonderheide, Robert H (Contact); Maity, Amit; Minn, Andy J; Wherry, E John	University of Pennsylvania
P01CA217797	Exploiting Redox Metabolism Using Pharmacological Ascorbate for Cancer Therapy	Cullen, Joseph J (Contact); Spitz, Douglas Robert	The University of Iowa
P01CA217798	Pancreatic Cancer Metastasis	Batra, Surinder K	University of Nebraska Medical Center
P01CA67166	Tumor Hypoxia: Molecular Studies and Clinical Exploitation	Giaccia, Amato J	Stanford University
P01CA80124	Integrative Pathophysiology of Solid Tumors	Jain, Rakesh K	Massachusetts General Hospital
P01CA84203	Molecular Response and Imaging-based Combination Strategies for Optimal PDT	Hasan, Tayyaba (Contact); Pogue, Brian W	Massachusetts General Hospital
P01CA94237	Enhancing T Cell Therapy of Cancer	Heslop, Helen E (Contact); Rooney, Cliona M	Baylor College of Medicine
P20CA192994	1/2: Feasibility Studies to Build Collaborative Partnerships in Reducing Racial/Ethnic Disparities in GI Cancer Research Minority Supplement 1	Li, Ellen	State University New York at Stony Brook
P20CA192996	2/2 Partnership to Study Racial/Ethnic Differences in GI Cancer Biology	McCombie, William Richard	Cold Spring Harbor Laboratory
P20GM103480	Nebraska Center for Nanomedicine	Bronich, Tatiana K	University of Nebraska Medical Center

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P20GM109024	Center for Diagnostic and Therapeutic Strategies in Pancreatic Cancer	Mallik, Sanku	North Dakota State University
P30CA13330	Core Support for Cancer Center	Goldman, Israel David	Albert Einstein College of Medicine, Inc.
P30CA15704	Cancer Center Support Grant	Gilliland, D Gary	Fred Hutchinson Cancer Research Center
P30CA16520	Abramson Cancer Center Support Grant	Dang, Chi V	University of Pennsylvania
P30CA36727	Fred & Pamela Buffett Cancer Center Support Grant	Cowan, Kenneth H	University of Nebraska Medical Center
P30CA46592	University of Michigan Comprehensive Cancer Center Support Grant	Fearon, Eric R	University of Michigan at Ann Arbor
P30CA56036	Translational Research in Cancer	Knudsen, Karen E	Thomas Jefferson University
P30CA68485	Cancer Center Support Grant	Pietenpol, Jennifer A	Vanderbilt University Medical Center
P41EB24495	Resource for Molecular Imaging Agents in Precision Medicine	Pomper, Martin G	Johns Hopkins University
P50AA11999	Southern California Research Center for ALPD and Cirrhosis	Tsukamoto, Hidekazu	University of Southern California
P50CA102701	Mayo Clinic SPORE in Pancreatic Cancer	Petersen, Gloria M (Contact); Billadeau, Daniel D	Mayo Clinic Rochester
P50CA127003	SPORE: Df/Hcc Spore in Gastrointestinal Cancer	Bass, Adam Joel (Contact); El-Bardeesy, Nabeel	Dana–Farber Cancer Institute
P50CA127297	SPORE in Pancreatic Cancer	Hollingsworth, Michael A	University of Nebraska Medical Center
P50CA130810	Translational Research in GI Cancer	Brenner, Dean E	University of Michigan at Ann Arbor
P50CA196510	Washington University SPORE in Pancreatic Cancer	Hawkins, William G	Washington University

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P50CA62924	SPORE in Gastrointestinal Cancer	Klein, Alison P	Johns Hopkins University
R00CA158582	Role of Epigenetic Regulators in Pancreatic Cancer	Tzatsos, Alexandros	The George Washington University
R01AA24698	Alcohol Carcinogenesis	Srivastava, Rakesh K	Louisiana State University Health Sciences Center
R01AA24770	A Pooling Project on Alcohol Use and Risk of Cancers with Inconsistent Prior Evidence, with an Emphasis in Non-smokers.	Ferrari, Pietro (Contact); Smith-Warner, Stephanie A	International Agency for Research on Cancer
R01AI58072	Structural Basis for Chemokine Function	Volkman, Brian F	Medical College of Wisconsin
R01AR60209	FoxO Signaling and Skeletal Muscle Atrophy	Judge, Andrew Robert	University of Florida
R01AT7448	Oxidative Stress and Programmed Death Pathways: Crosstalk in Pancreatic Cancer	Kumar, Addanki Pratap	The University of Texas Health Science Center
R01CA100062	Mechanism of Myeloid Cell Defect in Cancer	Gabrilovich, Dmitry I	The Wistar Institute
R01CA104125	Cytoskeletal Dynamics in Pancreatic Cancer Metastasis	McNiven, Mark A (Contact); Razidlo, Gina Lynn	Mayo Clinic Rochester
R01CA112314	Mechanism and Anti-Cancer Activity of SCFA-Hexosamine Analogs	Yarema, Kevin J	Johns Hopkins University
R01CA116034	Regulation of K-Ras by a Farnesyl-electrostatic Switch	Philips, Mark Reid	New York University School of Medicine
R01CA118374	Calcineurin-NFAT Regulates Endothelial Activation in Pre-metastatic Sites	Ryeom, Sandra W	University of Pennsylvania
R01CA120409	Immunotherapy with Car T Cells	June, Carl H (Contact); Zhao, Yangbing	University of Pennsylvania
R01CA123031	Dynamic requirements of Ras signaling during cancer	Counter, Christopher M	Duke University
R01CA124586	Kras-Induced Cellular Plasticity in Pancreatic Cancer	Konieczny, Stephen F	Purdue University

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R01CA124723	The Inhibition of HSP70 Induces Apoptosis in Pancreatic Cancer Cells	Saluja, Ashok K	University of Miami School of Medicine
R01CA129105	Cell Growth Signaling in Cancer Development	Sabatini, David M	Whitehead Institute for Biomedical Research
R01CA131045	ATDC Function in Human Pancreatic Adenocarcinoma	Simeone, Diane M	University of Michigan at Ann Arbor
R01CA132755	Molecular Mechanisms of BRCA1-Dependent DNA Damage Response and Tumorigenesis	Yu, Xiaochun	Beckman Research Institute/City of Hope
R01CA135274	Overcoming Pancreatic Tumor Resistance to Gemcitabine	Cui, Zhengrong	The University of Texas at Austin
R01CA135650	Predictive Cancer Diagnostics and Therapy Response	Moore, Anna (Contact); Medarova, Zdravka O	Massachusetts General Hospital
R01CA136526	Mechanism of Pancreatic Carcinogenesis	Fernandez-Zapico, Martin Ernesto	Mayo Clinic Rochester
R01CA138441	Mechanisms of MEK/ERK Growth Arrest Signaling	Park, Jong-In	Medical College of Wisconsin
R01CA142669	Fluorophore-Conjugated Antibodies for Imaging and Resection of GI Tumors	Bouvet, Michael (Contact); Yang, Meng	University of California, San Diego
R01CA150190	Targeting Pancreatic Cancer Using Peptide Chemistry: From Bench to Bedside (MPDPI R01 CA150190 Competitive Renewal 2015)	Mukhopadhyay, Debabrata (Contact); Spaller, Mark R	Mayo Clinic, Jacksonville
R01CA151588	Mechanisms of Pancreatic Inflammation, Tissue Repair and Carcinogenesis	Pasca Di Magliano, Marina	University of Michigan at Ann Arbor
R01CA154451	Ultrasound Enhanced Penetration for Treatment of Pancreatic Cancer	Hwang, Joo Ha	University of Washington
R01CA154586	The Anti-senescence Activity of Trefoil Factor 1	Wang, Xiao-Fan	Duke University
R01CA154649	The Role of Entosis in Human Cancers	Overholtzer, Michael H	Sloan-Kettering Institute

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R01CA154823	Validation and Fine-Scale Mapping of Pancreatic Cancer Susceptibility Loci	Klein, Alison P	Johns Hopkins University
R01CA155117	Mutual Regulation of PTEN and P-REX2a in Normal and Cancer Cells	Parsons, Ramon E	Icahn School of Medicine at Mount Sinai
R01CA155198	Design of MEK Inhibitor Regimens for the Treatment of Pancreatic Cancer	Leopold, Judith S	University of Michigan at Ann Arbor
R01CA155620	RON Receptor in Pancreatic Cancer Biology and Therapy	Lowy, Andrew M	University of California, San Diego
R01CA157490	Investigating the Role of Autophagy in Pancreatic Cancer Radiation Resistance	Kimmelman, Alec	New York University School of Medicine
R01CA157738	Novel Single Domain Antibodies with Multivalency and Multispecificity	Liu, Rihe	The University of North Carolina at Chapel Hill
R01CA159222	ADAM17 in Pancreatitis and Pancreatic Cancer	Crawford, Howard C	University of Michigan at Ann Arbor
R01CA160417	Targeting HMGB1-Mediated Autophagy in Cancer Therapy	Tang, Daolin	University of Pittsburgh at Pittsburgh
R01CA161112	Overcoming Stromal Barriers to Therapeutics in Pancreas Cancer	Hingorani, Sunil R	Fred Hutchinson Cancer Research Center
R01CA161283	N-3 Fatty Acid-Induced Akt Suppression: Chemoprevention for Pancreatic Neoplasia	Grippo, Paul J	University of Illinois at Chicago
R01CA161976	Stat3 Signaling in Pancreas Cancer	Merchant, Nipun B	University of Miami School of Medicine
R01CA163441	Radiotherapy as Immunotherapy of Tumors	Strober, Samuel	Stanford University
R01CA163489	Characterization of lcmt in Animal Models of Cancer	Philips, Mark Reid	New York University School of Medicine
R01CA163541	Exploiting Tumor Stroma Interactions for Cancer Therapy	Powis, Garth	Sanford Burnham Prebys Medical Discovery Institute
R01CA163649	Targeting MUC1-Induced Tumor-stromal Metabolic Cross-talk in Pancreatic Cancer	Singh, Pankaj Kumar	University of Nebraska Medical Center

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R01CA163698	Dissection and Manipulation of RB Function	Dyson, Nicholas J	Massachusetts General Hospital
R01CA163764	Sigma-2/Peptidomimetic Conjugates Target Apoptosis in Pancreatic Cancer	Hawkins, William G	Washington University
R01CA163798	IKK Alpha, Autophagy, Obesity and Injury Enhanced Pancreatic Cancer	Karin, Michael	University of California, San Diego
R01CA163895	Selective Sensitization of Pancreatic Cancer to Therapy by Chk1 and PARP1 Inhibit	Morgan, Meredith A	University of Michigan at Ann Arbor
R01CA164041	Aldo-keto Reductase Family 1 Member B10 AKR1B10 in Pancreatic Carcinogenesis	Yang, Guang-Yu	Northwestern University
R01CA164964	Prospective Study of Human Oral Microbiome and Pancreatic Cancer Risk	Ahn, Jiyoung	New York University School of Medicine
R01CA166150	Microbiomes in Human Pancreatic Cancer	Michaud, Dominique S	Tufts University Boston
R01CA167174	The Role of Fibroblasts in the Activities of Tissue Penetrating Peptides	Sugahara, Kazuki	Columbia University Health Sciences
R01CA167291	Novel Role of Ref-1 in Pancreatic Cancer Etiology and Progression	Kelley, Mark R (Contact); Fishel, Melissa L	Indiana University-Purdue University at Indianapolis
R01CA167535	Novel Nanoparticle Therapy for Pancreatic Cancer	Matters, Gail L (Contact); Kester, Mark	Pennsylvania State University Hershey Medical Center
R01CA168448	Next Generation Oncolytic Adenovirus for Advanced Pancreatic Cancer Treatment	Yamamoto, Masato	University of Minnesota
R01CA168611	Toll-like Receptor Regulation of Pancreatic Tumorigenesis	Miller, George	New York University School of Medicine
R01CA168692	Targeting a Non-canonical RAS-driven Pathway in Pancreatic Cancer	Cheresh, David A	University of California, San Diego
R01CA168712	Highly Specific and Efficient Vectors for Targeting Pancreatic Cancer	Kelly, Kimberly A (Contact); French, Brent A; Logsdon, Craig D	University of Virginia
R01CA168863	Ccr2 Blockade in Human Pancreatic Cancer	Linehan, David C	University of Rochester

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R01CA169046	The Chemical Biology of Pharmacological Ascorbate in Cancer Treatment	Buettner, Garry R	University of Iowa
R01CA169086	PDG Links Stem Cell Niche to Pancreatic Epithelial Renewal, Repair and Cancer	Thayer, Sarah P	University of Nebraska Medical Center
R01CA169122	Genetic Susceptibility and Risk Model for Pancreatic Cancer	Wei, Peng	The University of Texas Health Science Center at Houston
R01CA169123	Immunobiology and Immunotherapy of Pancreatic Cancer	Vonderheide, Robert H (Contact); Stanger, Ben Z	University of Pennsylvania
R01CA169134	HLTF Gene Silencing: a Novel Determinant of Sensitivity to Autophagy Inhibition	Amaravadi, Ravi K	University of Pennsylvania
R01CA169281	Targeting Stromal Collagen in Pancreatic Cancer	Han, Haiyong (Contact); Von Hoff, Daniel D	Translational Genomics Research Institute
R01CA169702	Annexin A2 as a Mediator of Pancreatic Cancer Metastases	Zheng, Lei	Johns Hopkins University
R01CA169774	Detection of *In Vivo* Enzyme Activities with CEST MRI	Cardenas-Rodriguez, Julio	The University of Arizona
R01CA170946	Triptolide Augments Death Receptor Mediated Apoptosis in Pancreatic Cancer	Saluja, Ashok K	University of Miami School of Medicine
R01CA172045	Epigenetic Regulation of Pancreatic Cancer	Hebrok, Matthias	University of California, San Francisco
R01CA172233	Molecular Mediators of Pancreatic Cancer Invasion and Progression	Xie, Keping	The University of Texas MD Anderson Cancer Center
R01CA172431	Inhibition of Pancreatic Carcinogenesis via Targeting c-Raf and sEH	Yang, Guang-Yu	Northwestern University
R01CA172560	Mechanisms of Action of the Smyd3 Methyltransferase in Cancer Cells	Gozani, Or P (Contact); Sage, Julien	Stanford University
R01CA172880	Dicarbonyl Stress, Advanced Glycation End Products and Risk of Pancreatic Cancer	Jiao, Li	Baylor College of Medicine

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R01CA174294	Multifunctional ImmunoPET Tracers for Pancreatic and Prostate Cancer	Wu, Anna M (Contact); Reiter, Robert E	University of California, Los Angeles
R01CA174388	Single-Cell Phenotyping for Therapeutic Stratification in Pancreatic Cancer	Wirtz, Denis	Johns Hopkins University
R01CA174768	Understanding Optimal Delivery Systems for Cancer Care	Miller, David C	University of Michigan at Ann Arbor
R01CA174861	Novel Theranostics for Pancreatic Cancer	Davydova, Julia	University of Minnesota
R01CA175495	The B7x Pathway in the Tumor Microenvironment	Zang, Xingxing	Albert Einstein College of Medicine
R01CA175747	Mechanisms of PAK1 Activation, Signaling and Tumor Resistance	Der, Channing J (Contact); Hahn, Klaus M	The University of North Carolina at Chapel Hill
R01CA175772	Targeting Tumor-Stromal Interaction for Pancreatic Cancer Therapy	Singh, Ajay Pratap	University of South Alabama
R01CA176647	Mutant p53 as Actionable Cancer-Specific Target	Moll, Ute Martha	State University of New York at Stony Brook
R01CA176828	Using Markers to Improve Pancreatic Cancer Screening	Goggins, Michael G	Johns Hopkins University
R01CA177670	Reprogramming the Metastatic Microenvironment of Pancreatic Cancer Through Csf1r	Denardo, David G	Washington University
R01CA177857	Role of Neurogenic Inflammation in Pancreatic Cancer	Davis, Brian M	University of Pittsburgh at Pittsburgh
R01CA178015	Crucial Microenvironmental Cofactors for Pancreatic Cancer Pathogenesis	Collisson, Eric	University of California, San Francisco
R01CA178445	The Role of Wild-Type KRAS in the Context of Tumor Profession and Metastasis	Su, Gloria Huei-Ting	Columbia University Health Sciences
R01CA178627	Novel Experimental Therapeutics for Pancreatic Cancer	Lomberk, Gwen	Mayo Clinic, Rochester

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R01CA179645	Mechanisms and Targeting Of SWI/SNF Alterations in Pancreatic Cancer	Pollack, Jonathan R	Stanford University
R01CA179991	(PQB6) Genetics of Subclonal Evolution in Pancreatic Cancer	Iacobuzio-Donahue, Christine A	Sloan-Kettering Institute
R01CA180057	(PQD6) Muscle Stem Cells and Cancer Cachexia	Guttridge, Denis C	The Ohio State University
R01CA180949	Early Detection of Pancreatic Cancer in Diabetics	Chen, Ru (Contact); Pan, Sheng	University of Washington
R01CA181185	Inhibition of CDC25B Phosphatase by Targeting Protein-Protein Interactions	Cierpicki, Tomasz	University of Michigan at Ann Arbor
R01CA181244	Discovery of Risk Loci and Genomics of Pancreatic Cancer through Exome Sequencing	Scheet, Paul A (Contact); Huff, Chad Daniel	The University of Texas MD Anderson Cancer Center
R01CA181360	Clustered Semi-Competing Risks Analysis in Quality of End-of-life Care Studies	Haneuse, Sebastien	Harvard T.H. Chan School of Public Health
R01CA181385	Stellate Cells and Their Progenitor Precursors in Pancreas Cancer Progression	Provenzano, Paolo	University of Minnesota
R01CA181450	Pancreatic Ductal Adenocarcinoma Is a Disease of Constitutive Autophagy	Zeh, Herbert J (Contact); Lotze, Michael T	University of Pittsburgh at Pittsburgh
R01CA182076	Biomarker Validation for Intraductal Papillary Mucinous Neoplasms of the Pancreas	Allen, Peter J (Contact); Fernandez-Del Castillo, Carlos ; Wolfgang, Christopher L	Sloan-Kettering Institute
R01CA182311	High Dose Radiation Therapy to Direct Immune Responses to Pancreatic Cancer	Gough, Michael James	Providence Portland Medical Center
R01CA182495	Fingerprinting Invasive Membrane Protrusions to Discover Metastatic Signatures	Klemke, Richard L	University of California, San Diego
R01CA182869	The Role of DCLK1 in the Initiation of Pancreatic Ductal Adenocarcinoma	Houchen, Courtney Wayne	The University of Oklahoma Health Sciences Center
R01CA183101	Biophotonics to Couple Pancreatic with Upper GI	Backman, Vadim (Contact); Rogers,	Northwestern University

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	Screening via Ultrathin Endoscopy	Jeremy D; Roy, Hemant K	
R01CA183459	Targeting Mucin and EGFR Axis in Pancreatic Cancer	Batra, Surinder K	University of Nebraska Medical Center
R01CA183984	A Novel miR-198 Replacement Therapy for Pancreatic Cancer	Yao, Qizhi C	Baylor College of Medicine
R01CA184051	Pharmacological Ascorbate as a Radiosensitizer in Pancreatic Cancer	Cullen, Joseph J	The University of Iowa
R01CA184274	Functional Significance of CD133 in Pancreatic Cancer	Banerjee, Sulagna	University of Miami School of Medicine
R01CA184926	(PQB-3) Driver Gene-Induced Inflammation in Pancreatic Cancer Development	Jaffee, Elizabeth M	Johns Hopkins University
R01CA185357	(PQD3)Molecular Profiles Associated with Long-Term Survival in Pancreas Cancer	Ahuja, Nita (Contact); Easwaran, Hariharan; Iacobuzio-Donahue, Christine A	Johns Hopkins University
R01CA186043	Musashi-Mediated Control of Pancreatic Cancer Growth and Progression	Reya, Tannishtha (Contact); Lowy, Andrew M	University of California, San Diego
R01CA186286	Pancreatic Cancer Cell Mechanics and Imaging	Konstantopoulos, Konstantinos	Johns Hopkins University
R01CA186338	ZIP4 Is a Novel Molecular Target in Human Pancreatic Cancer	Li, Min (Contact); Fernandez-Zapico, Martin Ernesto	The University of Oklahoma Health Sciences Center
R01CA186662	Novel Small Molecule MDM2 Inhibitors for Pancreatic Cancer Therapy	Zhang, Ruiwen	Texas Tech University Health Sciences Center
R01CA186885	Targeting BET Bromodomain in Pancreatic Cancer	Munshi, Hidayatullah G	Northwestern University
R01CA187090	The Yap-Tead Transcriptional Complex in Kras-Induced Pancreatic Ductal Adenocarci	Yi, Chunling	Georgetown University
R01CA187678	PET Imaging-Guided Personalized Therapy in Pancreatic Cancer	Radu, Caius Gabriel (Contact); Czernin, Johannes; Donahue, Timothy R	University of California, Los Angeles

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R01CA187923	Novel Strategies to Potentiate a Ras-Targeted Oncolytic Herpes Simplex Virus	Zhang, Xiaoliu	University of Houston
R01CA188048	Investigating a Novel Glutamine Metabolism Pathway in Pancreatic Cancer	Kimmelman, Alec	Dana–Farber Cancer Institute
R01CA188134	Nrf2 Regulation of Ductal Pancreatic Cancer Etiology and Treatment Response	Tuveson, David A	Cold Spring Harbor Laboratory
R01CA188252	ROS-Targeted Therapy for Pancreatic Cancer	Neamati, Nouri	University of Michigan at Ann Arbor
R01CA188300	Motion Management of Pancreatic Cancer in MRI-Guided Radiotherapy	Sheng, Ke	University of California, Los Angeles
R01CA188430	Synergistic Targeting of Cholesterol Metabolism and EGFR Signaling in Cancer	Astsaturov, Igor	Research Institute of Fox Chase Cancer Center
R01CA188464	Epigenetic Priming in Pancreatic Cancer Chemotherapy	Govindarajan, Rajgopal	The Ohio State University
R01CA188654	MR-HIFU Induced Drug Delivery for Pancreatic Cancer Treatment	Lee, Donghoon	University of Washington
R01CA189209	Radio-immunotherapy to Target Cancer Stem Cells in Solid Tumor Malignancies	Murphy, William Joseph	University of California, Davis
R01CA190092	(PQA-4) Organoid Omics to Detect and Defeat Ductal Pancreatic Cancer	Tuveson, David A	Cold Spring Harbor Laboratory
R01CA190408	Drugging the Switch-II Pocket of K-Ras	Shokat, Kevan M	University of California, San Francisco
R01CA190717	Alternatively Spliced Tissue Factor and Pathobiology of Pancreatic Cancer	Bogdanov, Vladimir	University of Cincinnati
R01CA191191	IDO2 Targeting in Pancreatic Cancer	Prendergast, George C	Lankenau Institute for Medical Research
R01CA192381	Exploitation of RAS Signaling to Develop Therapy and Early Detection Strategies for PDA	Brekken, Rolf A (Contact); Wilkie, Thomas M	UT Southwestern Medical Center

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R01CA193365	Molecular Imaging of Cachexia in Pancreatic Cancer	Bhujwalla, Zaver M	Johns Hopkins University
R01CA193650	The Adaptive Kinome In Pancreatic Cancer	Yeh, Jen Jen (Contact); Johnson, Gary L	The University of North Carolina at Chapel Hill
R01CA193887	Targeting Extracellular Matrix-Cancer Stem Cell Interactions in Pancreatic Cancer	Matsui, William H	Johns Hopkins University
R01CA193895	Glutaminase Inhibitor Drug Discovery and Nanoparticle-Based Delivery for Pancreatic Cancer Therapy	Slusher, Barbara Stauch (Contact); Hanes, Justin S; Le, Anne	Johns Hopkins University
R01CA194321	Imaging Drug Uptake and Distribution in Chemoradiation Therapy of Pancreatic Cancer	Humm, John L (Contact); Lowery, Maeve Aine; Wu, Abraham	Sloan-Kettering Institute
R01CA194593	PQB3: Mechanisms & Targeting of Sonic Hedgehog Signaling in Muscle Wasting of Cancer Cachexia	Zimmers, Teresa A	Indiana University-Purdue University at Indianapolis
R01CA194941	Suppression of Pancreatic Tumorigenesis by the PTF1 Transcription Factor Network	Murtaugh, Lewis C (Contact); Macdonald, Raymond J	The University of Utah
R01CA195473	Repurposing Disulfiram: A Novel Strategy to Help Cancer Patients Regain Muscle	Jatoi, Aminah (Contact); Fernandez-Zapico, Martin Ernesto	Mayo Clinic, Rochester
R01CA195586	Targeted Radiation Therapy for Pancreatic Cancer	Batra, Surinder K (Contact); Jain, Maneesh	University of Nebraska Medical Center
R01CA195651	Clinical Significance of Pancreatic Cancer Differentiation and Dedifferentiation	Xie, Keping	The University of Texas MD Anderson Cancer Center
R01CA195708	Molecular Mechanism of Bitter Melon Juice Efficacy Against Pancreatic Cancer	Agarwal, Rajesh	University of Colorado Denver
R01CA195733	Employing Mouse Models to Translate Early Detection of Pancreas Cancer	Kalluri, Raghu (Contact); Worms, David	The University of Texas MD Anderson Cancer Center

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R01CA196215	Systemic Therapy with Infectivity-Selective Oncolytic Adenovirus for PDAC	Yamamoto, Masato	University of Minnesota
R01CA196228	The Role of Post-translational Activation of Myc in Pancreatic Cancer	Sears, Rosalie C	Oregon Health & Science University
R01CA196286	Validation of Pancreatic Cancer Biomarkers in Large Prospective Cohorts	Lokshin, Anna E	University of Pittsburgh at Pittsburgh
R01CA196941	Novel Signaling Pathways Regulating Pancreatic Cancer Pathogenesis	Wang, Huamin	The University of Texas MD Anderson Cancer Center
R01CA197296	Reprogramming the Pancreatic Tumor Microenvironment with Immunotherapy	Zheng, Lei (Contact); Jaffee, Elizabeth M	Johns Hopkins University
R01CA197916	Targeting Macrophages for Immunotherapy in Pancreatic Cancer	Beatty, Gregory L	University of Pennsylvania
R01CA197999	Development of Quinoxaline Based IKK Beta Inhibitors for Kras Driven Cancers	Natarajan, Amarnath	University of Nebraska Medical Center
R01CA198074	Dosage-Dependent Hedgehog Signaling in Pancreatic Cancer	Allen, Benjamin (Contact); Pasca Di Magliano, Marina	University of Michigan at Ann Arbor
R01CA198090	Integrated Signaling in Pancreatic Cancer Progression	Xie, Keping	The University of Texas MD Anderson Cancer Center
R01CA198095	Novel Strategies for Precision T-Cell Therapies	Almo, Steven C	Albert Einstein College of Medicine
R01CA198096	Tumor Priming Sequences Combined with Novel Nanoparticle Drug Carriers for Enhanced Therapeutic Efficacy in Pancreatic Cancer: A Tripartite USA/Northern Ireland/Republic of Ireland Consortium	Straubinger, Robert M (Contact); Barron, Niall; Ma, Wen Wee; Scott, Chris	State University of New York at Buffalo
R01CA198128	Exploiting Caveolae-Dependent Albumin Endocytosis to Optimize Therapy in Pancreatic Cancer	Williams, Terence Marques	The Ohio State University

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R01CA199064	Tumor Subtypes and Therapy Response in Pancreatic Cancer	Yeh, Jen Jen (Contact); Graves, Lee M; Johnson, Gary L	The University of North Carolina at Chapel Hill
R01CA199646	Optimizing Ultrasound Enhanced Delivery of Therapeutics	Forsberg, Flemming	Thomas Jefferson University
R01CA200007	Multiplexed Imaging of Biliary Intra-Epithelial Neoplasia	Seibel, Eric J (Contact); Wang, Thomas D	University of Washington
R01CA200572	PKD1 Signaling in the Initiation of Pancreatic Cancer	Storz, Peter	Mayo Clinic, Jacksonville
R01CA200755	Exploring the Role of Mitochondrial Fission in Pancreatic Tumorigenesis	Kashatus, David Francis	University of Virginia
R01CA201226	High Throughput Screening to Discover Chemical Inhibitors of Quiescin Sulfhydryl Oxidase 1	Faigel, Douglas (Contact); Sergienko, Eduard A	Mayo Clinic, Arizona
R01CA201318	The Paradoxical Role of mTORC1 in the Growth of Nutrient-Deprived Pancreatic Cancer Cells Harboring Ras Mutations	Thompson, Craig B	Sloan-Kettering Institute
R01CA202762	Pharmacogenomic and Circulating Tumor Cell Approach to Individualized Treatment of Pancreatic Cancer	Yu, Kenneth H (Contact); Ricigliano, Mark	Sloan-Kettering Institute
R01CA202846	Targeted Therapy of Peritoneal Carcinomatosis Using Theranostic Nanoparticles	Yang, Lily (Contact); Mao, Hui ; Wang, Y Andrew	Emory University
R01CA202917	JAK1 Signaling in Pancreatic Cancer Initiation and Progression	Wagner, Kay-Uwe	University of Nebraska Medical Center
R01CA203108	Prognostic Biomarkers for ZIP4-mediated Cachexia in Pancreatic Cancer	LI, Min (Contact); Li, Yi-Ping	The University of Oklahoma Health Sciences Center
R01CA203737	Targeting Human Cancers with Hemizygous Deletion of TP53	Lu, Xiongbin	The University of Texas MD Anderson Cancer Center
R01CA203890	Combined Tumor and Stromal Targeting to Improve	Denardo, David G	Washington University

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	Pancreatic Cancer Response to Immunotherapy		
R01CA204228	Comprehensive Genetic Dissection of Druggable KRAS Targets	Leach, Steven D	Sloan-Kettering Institute
R01CA204969	Uncovering Role of Exosomes in Regulating Pancreatic Cancer Cell Metabolism	Nagrath, Deepak	Rice University
R01CA206069	Development of Targeted Nanotechnology Platform for Pancreatic Cancer	Chauhan, Subhash C	The University of Tennessee Health Sciences Center
R01CA206105	Regulation of Pancreatic Oncogenesis by the Gut Microbiome	Miller, George (Contact); Saxena, Deepak	New York University School of Medicine
R01CA206444	Rac1 GTPase in Tumorigenesis and Progression of Pancreatic Cancer	Ouellette, Michel M (Contact); Batra, Surinder K	University of Nebraska Medical Center
R01CA207031	The Molecular Mechanisms of Metabolism Reprogramming in Mutant Kras/Ink4a-Driven Pancreatic Ductal Adenocarcinoma	Chiao, Paul J	The University of Texas MD Anderson Cancer Center
R01CA207110	Prospective Immune Profiling Using Methylation Markers and Pancreatic Cancer Risk	Michaud, Dominique S (Contact); Kelsey, Karl Timothy	Tufts University Boston
R01CA207189	Regulation of Nutrient Stress-Induced Macropinocytosis in Pancreatic Ductal Adenocarcinoma	Commisso, Cosimo	Sanford Burnham Prebys Medical Discovery Institute
R01CA207236	Fasting Protects Small Intestinal Stem Cells from Lethal DNA Damage: Mechanistic Insight and Preclinical Translation	Piwnica-Worms, Helen M	The University of Texas MD Anderson Cancer Center
R01CA207643	Real-Time Monitoring of Circulating Pancreatic Tumor Cells and Clusters	Carpenter, Erica	University of Pennsylvania
R01CA208108	MUC16 in Pancreatic Cancer Progression and Metastasis	Radhakrishnan, Prakash	University of Nebraska Medical Center
R01CA208205	Reengineering Obesity-Induced Abnormal	Fukumura, Dai (Contact); Jain, Rakesh K	Massachusetts General Hospital

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	Microenvironment to Improve PDAC Treatment		
R01CA208253	Enhancing Immune Therapy in Pancreatic Cancer by Targeting IL-6	Lesinski, Gregory B	The Ohio State University
R01CA208272	Developing Novel Combination Therapies for Pancreatic Cancer	Yoon, Karina J	The University of Alabama at Birmingham
R01CA208335	Label Free Microfluidic Isolation, Characterization and *Ex Vivo* Expansion of CTCs	Nagrath, Sunitha	University of Michigan at Ann Arbor
R01CA208401	Protein and Proteolytic Activity Biomarkers of Early-Stage Pancreatic Cancer	Tempst, Paul (Contact); Yu, Kenneth H	Sloan-Kettering Institute
R01CA208514	Mechanisms of Durable Antitumor Immunity via CD26hiCD4+ T Cells	Paulos, Chrystal Mary	Medical University of South Carolina
R01CA208517	Determinants of Pancreatic Cancer and Malignant Melanoma Phenotypes in CDKN2A Hereditary Kindreds	Petersen, Gloria M (Contact); Fernandez-Zapico, Martin Ernesto; Li, Hu	Mayo Clinic, Rochester
R01CA208644	(PQ11) Targeting STING in the Context of Chemoradiation Therapy to Overcome Poor Preexisting Immunity in Mouse Models of Pancreatic Cancer	Crittenden, Marka	Providence Portland Medical Center
R01CA209798	Investigating the Cause of Racial/Ethnic Disparity in Pancreatic Cancer Incidence	Setiawan, Veronica Wendy	University of Southern California
R01CA209886	MRI-Guided Dendritic-Cell-Based Vaccine Immunotherapy for Pancreatic Cancer	Zhang, Zhuoli	Northwestern University
R01CA210192	Targeted Nanotherapy for Pancreatic Cancer	Chauhan, Subhash C	The University of Tennessee Health Sciences Center
R01CA210439	Targeting the Metabolic Basis of Cachexia in Pancreatic Cancer	Singh, Pankaj Kumar	University of Nebraska Medical Center
R01CA210553	Image-Guided Ultrasound Therapy and Drug Delivery in Pancreatic Cancer	Ferrara, Katherine W	University of California, Davis

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R01CA210637	Role of PD2/Paf1 in Pancreatic Acinar to Ductal Metaplasia	Ponnusamy, Moorthy P (Contact); Batra, Surinder K	University of Nebraska Medical Center
R01CA211070	The Pancreatic Cancer Microenvironment	Kang, Rui	University of Pittsburgh at Pittsburgh
R01CA211082	Optical Imaging of Pancreas Cancer Organoids for Drug Development and Personalized Treatment	Skala, Melissa Caroline	Morgridge Institute for Research, Inc.
R01CA211087	Noninvasive Prediction of Tumor Response to Gemcitabine Using MRI	Liu, Guanshu	Hugo W. Moser Research Institute Kennedy Krieger
R01CA211098	Thrombin-Dependent Mechanisms of Pancreatic Ductal Adenocarcinoma Disease	Flick, Matthew J (Contact); Konieczny, Stephen F	Cincinnati Children's Hospital Medical Center
R01CA211176	Preclinical Analyses of NAD Kinase as a Redox Vulnerability for the Treatment of Pancreatic Cancer	Elsea, Sarah H	Baylor College of Medicine
R01CA211554	First in Human Study with 18F-avb6 Targeting Peptide	Sutcliffe, Julie L	University of California, Davis
R01CA211687	Role of Nonsense Mediated RNA Decay in Pancreatic Cancer	Philips, Mark Reid	New York University School of Medicine
R01CA211720	Synthetic Lethal Targeting of Growth Factor Receptors	Peterson, Blake	University of Kansas Lawrence
R01CA211752	Heparinase in Tumor Progression, Metastasis and Chemoresistance	Sanderson, Ralph D	The University of Alabama at Birmingham
R01CA211878	Common Genetically Altered Pathways as Targets for Therapy in Pancreatic Cancer	Witkiewicz, Agnieszka (Contact); Knudsen, Erik	The University of Arizona
R01CA211927	Reconstituting Human Pancreatic Cancer Development for Translational Research	Kim, Seung K	Stanford University
R01CA212086	Optimizing the Treatment of Pancreatic Adenocarcinoma	Hur, Chin	Massachusetts General Hospital

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R01CA212350	Stroma Targeted Theranostic Nanoparticles for Pancreatic Cancer	McNally, Lacey R	Wake Forest University Health Sciences
R01CA212600	Targeting HuR to Improve a Synthetic Lethal Therapy for Pancreatic Cancer	Brody, Jonathan	Thomas Jefferson University
R01CA213233	Exosomes in Cancer Therapy	Kalluri, Raghu	The University of Texas MD Anderson Cancer Center
R01CA213278	Reprogramming Tumor Microenvironment by Nanoparticle	Mukherjee, Priyabrata	The University of Oklahoma Health Sciences Center
R01CA215471	Dectin-1 Signaling Drives Pancreatic Oncogenesis by Inducing Macrophage-Mediated Adaptive Immune Suppression	Miller, George	New York University School of Medicine
R01CA215607	Targeting Cysteine Import to Induce Ferroptotic Cell Death in Pancreatic Cancer	Olive, Kenneth P	Columbia University Health Sciences
R01CA216853	Metabolic Regulation of Tumor Progression, Metastasis and Chemoresistance by SIRT5/ELK3 Signaling in Pancreatic Cancer	Singh, Pankaj Kumar	University of Nebraska Medical Center
R01CA216879	Targeted Molecular Imaging of Plectin-1; Bench to Bedside and Back Again	Sutcliffe, Julie L (Contact); Kelly, Kimberly A	University of California, Davis
R01CA216987	Exploring Ras Sumoylation as a New Anti-Cancer Strategy	Dai, Wei (Contact); Chen, Yuan	New York University School of Medicine
R01CA217207	The Development and Progression of IPMN To PDA in the Context of Inactivated Activin Signaling	Su, Gloria Huei-Ting	Columbia University Health Sciences
R01CA217907	Galpha13 and Pancreatic Cancer Progression	Munshi, Hidayatullah G	Northwestern University
R01CA217989	Exosomes as Endocrine Signaling Molecules in Cancer Cachexia	Marks, Daniel L	Oregon Health & Science University
R01CA218004	Translational Applications in an Animal Model of Pancreatic Cystic Neoplasm and Cancer	Maitra, Anirban	The University of Texas MD Anderson Cancer Center

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R01CA218513	Development and Application of Asymmetric-Flow Field-Flow (AF4) Technology in Fractionation and Characterization of Exosome Subpopulations and Novel Nanovesicles in Pancreatic Cancer Model	Lyden, David Charles (Contact); Zhang, Haiying	Weill Medical College of Cornell University
R01CA219670	Targeting Novel Therapeutic Vulnerabilities in LKB1 Mutant Tumors	El-Bardeesy, Nabeel (Contact); Wong, Kwok Kin	Massachusetts General Hospital
R01CA220236	Wnt/?-catenin Signaling in Pancreatic Oncogenesis	Xie, Keping	The University of Texas MD Anderson Cancer Center
R01CA220237	UBAP2, a New Molecule in Pancreatic Cancer Progression	Mukherjee, Priyabrata	The University of Oklahoma Health Sciences Center
R01CA222049	Histopathologic Validation of 89Zr-DFO-HuMab-5B1 PET/CT Imaging in CA 19-9 Positive Pancreatic Cancer	Pandit Taskar, Neeta (Contact); D'Angelica, Michael I; Lewis, Jason S; Weber, Wolfgang	Sloan-Kettering Institute
R01CA222862	Tailoring Therapy to Pancreatic Cancer Subtypes	Collisson, Eric	University of California, San Francisco
R01CA222907	Development and Application of a Porcine Model of Pancreatic Cancer	Carlson, Mark A	University of Nebraska Medical Center
R01CA222930	Deregulation of COMPASS Complex and Enhancer Chromatin in Pancreatic Cancer	Tzatsos, Alexandros	The George Washington University
R01CA222969	Targeting Dectin-2 on Tumor-associated Macrophages for the Treatment of Cancer	Engleman, Edgar G	Stanford University
R01CA223204	Role of Lipocalin 2 in Pancreatic Cancer	Cruz-Monserrate, Zobeida	The Ohio State University
R01CA223483	Investigating the Metastatic Drive in Pancreas Cancer	Hingorani, Sunil R	Fred Hutchinson Cancer Research Center
R01CA224306	A Novel Molecular Cross-Talk Driving Pancreatic Cancer Progression	Singh, Ajay Pratap	University of South Alabama

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R01CA224763	Profiling Signaling Activity and Gene Expression in Single, Pancreatic Adenocarcinoma Cells Using CE-RNA-Seq	Allbritton, Nancy L (Contact); Lawrence, David S	The University of North Carolina at Chapel Hill
R01CA225637	Mechanism of APE1 in DNA Damage Response	Yan, Shan	The University of North Carolina at Charlotte
R01CA225955	Exploring Collateral Lethality for Development of Cancer Therapeutics	Depinho, Ronald Anthony	The University of Texas MD Anderson Cancer Center
R01CA227849	Redox Modification and Targeting of Mutant KRas in Cancer	Carroll, Kate Suzanne	Scripps Florida
R01CA228524	Targeting CXCR2 Axis in Pancreatic Cancer	Singh, Rakesh K (Contact); Batra, Surinder K	University of Nebraska Medical Center
R01CA229580	Identifying and Targeting Metabolic Dependencies in the Pancreatic Tumor Microenvironment	Sherman, Mara H	Oregon Health & Science University
R01CA229803	Molecular Determinants and Therapeutic Consequences of Immune Heterogeneity in Cancer	Vonderheide, Robert H (Contact); Stanger, Ben Z	University of Pennsylvania
R01CA33084	Mechanisms of Murine Tumor Eradication by Immunotherapy	Greenberg, Philip D	University of Washington
R01CA34610	TGFB-SMAD Signaling in Stem Cell Differentiation and Tumor Suppression	Massague, Joan	Sloan-Kettering Institute
R01CA42978	Biological Activity of Ras Oncogenes	Der, Channing J	The University of North Carolina at Chapel Hill
R01CA45726	Integrin Alpha V Beta 3 Promotes Resistance to EGF Receptor Inhibitors	Cheresh, David A	University of California, San Diego
R01CA51210	Biochemical and Molecular Studies on NQO1. Design of Less Toxic Hsp90 Inhibitors	Ross, David	University of Colorado Denver
R01CA54358	Epigenetic Drivers of Cancer Progression	Feinberg, Andrew P	Johns Hopkins University

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R01CA75059	Dysregulation of TGF Beta Action Pancreatic Cancer	Korc, Murray	Indiana University-Purdue University at Indianapolis
R01CA77575	Causes & Consequences of Acid pH in Tumors - Targeting Acidosis to Improve Immunotherapy in Pancreatic Cancer	Gillies, Robert J (Contact); Pilon-Thomas, Shari	H. Lee Moffitt Cancer Center and Research Institute
R01CA82683	Signal Transduction by Tyrosine Phosphorylation	Hunter, Tony R	Salk Institute for Biological Studies
R01CA94184	RalA Signal Transduction	Counter, Christopher M	Duke University
R01CA97022	Survival Mechanisms of Invasive Carcinoma Cells	Klemke, Richard L	University of California, San Diego
R01CA97061	Chemical Genetic Profiling of Engineered Tumor Cells	Stockwell, Brent R	Columbia University New York Morningside
R01CA98468	Improving CPT-11 Efficacy Using Structural and Chemical Biology	Redinbo, Matthew R	The University of North Carolina at Chapel Hill
R01DK106266	Development, Cellular Plasticity and Homeostasis of the Exocrine Pancreas	Sosa-Pineda, Beatriz	Northwestern University
R01DK107767	Omega-3 Derived Epoxy Fatty Acids and Seh In Pancreatitis-Induced Carcinogenesis	Yang, Guang-Yu	Northwestern University
R01DK110361	The Hippo Signaling Pathway in Pancreatic Epithelial Cells Orchestrate the Inflammatory Response	Wang, Pei	The University of Texas Health Science Center
R01DK52913	The Role of Zinc Finger Cofactors in Pancreatic Cell Growth	Urrutia, Raul A	Mayo Clinic, Rochester
R01DK55489	Pancreas Transcription Factors and Disease Model Systems	Konieczny, Stephen F	Purdue University
R01DK60694	Networks for Functional Regulation of Pancreatic Acinar-Ductal Metaplasia and Epithelial Plasticity	Rustgi, Anil K	University of Pennsylvania
R01DK61220	Transcriptional Regulators of the Exocrine Pancreatic Phenotype	MacDonald, Raymond J (Contact); Murtaugh, Lewis C	UT Southwestern Medical Center

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R01DK70888	Acinar Biology and Pancreatic Disease	Groblewski, Guy E	University of Wisconsin–Madison
R01EB17270	Light-Triggered Drug Release in Primed Pancreatic Tumors	Lovell, Jonathan F	State University of New York at Buffalo
R01EB17853	Polymeric Nanomedicines of Small Molecules and miRNA for Treating Pancreatic Cancer	Mahato, Ram I	University of Nebraska Medical Center
R01EB20125	Theranostic Nanoparticles for Detection and Treatment of Pancreatic Cancer	McNally, Lacey R	University of Louisville
R01EB24320	Surrogate Imaging Biomarkers for Tracking Anti-Stromal Therapy	Doyley, Marvin M	University of Rochester
R01EB25173	Endoscopic Fine-Needle Polarized Scanning Spectroscopy for Pancreatic Cystic Lesions Diagnosis	Perelman, Lev T	Beth Israel Deaconess Medical Center
R01EB25990	Deployable Ultrasound Applicators for MRI Guided Thermal Therapy of Pancreatic Cancer	Diederich, Chris John	University of California, San Francisco
R01EB26893	Controllable *In Vivo* Genome Editing for Immune-Checkpoint Blockade in Solid Tumors	Tong, Sheng	Rice University
R01GM105964	The Molecular Determinants of Zinc Uptake Mediated by hZIP4	Dempski, Robert Edward	Worcester Polytechnic Institute
R01GM111735	Phosphatidylinositol 4-Phosphate Hydrolysis in Spatiotemporal Cell Signaling	Smrcka, Alan V	University of Rochester
R01GM113166	Polymeric Nanomedicines of Hedgehog Inhibitor and miRNA for Treating Pancreatic Cancer	Mahato, Ram I (Contact); Batra, Surinder K	University of Nebraska Medical Center
R01GM126088	Lipid Regulation of Hypoxia-Inducible Factors	Espenshade, Peter J	Johns Hopkins University
R01GM66817	The Biochemical Basis for the Mechanics of Cytokinesis	Robinson, Douglas N	Johns Hopkins University
R01GM76186	ZIBER: Zombie-Silencing Induced by Error: A New Phenomenon in Genome Instability in Yeasts	Weinert, Ted A	The University of Arizona

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R01HD65800	Mechanisms Controlling Epithelial Homeostasis	O'Reilly, Alana M	Research Institute of Fox Chase Cancer Center
R03CA181727	A Novel Combination Approach for Pancreatic Cancer Prevention	Mackenzie, Gerardo Guillermo	State University New York at Stony Brook
R03CA182552	A Novel Regimen to Target Both Pancreatic Cancer K-Ras and Antiapoptotic Proteins	Li, Fengzhi	Roswell Park Cancer Institute Corporation
R03CA184544	Role of Piceatannol in Cancer Cachexia	Kim, Kee-Hong	Purdue University
R03CA191621	Developing a Screen for Novel Therapies with Reprogrammed Pancreatic Cancer Cells	Resar, Linda M S	Johns Hopkins University
R03CA195453	Endoenteric Balloon Coils for Improved MR Imaging of the Pancreas and Upper GI Tract	Hadley, John Rock	The University of Utah
R03CA201502	Multiplex Conditional Mice for Rapid and Affordable Pre-clinical Testing	Moriarity, Branden S	University of Minnesota
R03CA201738	Role of CRABP-II in Pancreatic Cancer Metastasis	Yu, Shuiliang (Contact); Zhou, Lan	Case Western Reserve University
R03CA208510	Interpreting Limits to Nanoparticle Delivery in High-Stroma Low-Perfusion Tumors	Russell, Stewart	Dartmouth College
R03CA212068	Epigenetic Regulation of Metabolic Reprogramming in Pancreatic Cancer	Tzatsos, Alexandros	The George Washington University
R03CA219725	IRF2BP2 Modification by Cdk5 Modulates Interferon-Gamma Response Tumor PD-L1 Level	Petrosiute, Agne	Case Western Reserve University
R03CA223619	Predicted Lean Body Mass, Fat Mass, and Risk of Lung, Pancreatic, Colorectal, Breast, and Prostate Cancers	Giovannucci, Edward	Harvard T.H. Chan School of Public Health
R03CA228007	Porphyromonas Gingivalis and Pancreatic Carcinogenesis in Mouse Models	Genco, Caroline A	Tufts University, Boston
R03CA231766	IL-15 TRiKES-Based Specific Immunotherapy of Pancreatic Ductal Adenocarcinoma	Ferrone, Soldano (Contact); Ferrone, Cristina R	Massachusetts General Hospital

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R13AA20691	International Symposium of ALPD and Cirrhosis	Tsukamoto, Hidekazu	University of Southern California
R13-DK118902	PancreasFest 2018 Early Diagnosis and Treatment of Pancreatitis, Pancreatic Diabetes and Pancreatic Cancer	Whitcomb, David Clement	University of Pittsburgh at Pittsburgh
R15CA195463	Cellular Pathways Affecting Oncolytic Virus-Host Interactions in Cancer	Grdzelishvili, Valery Zurabovich	The University of North Carolina at Charlotte
R15EB26208	Optimization of Aminolaevulinic Acid-Protoporphyrin IX for Fluorescence-Guided Tumor Resection and Treatment	Chen, Bin	University of the Sciences in Philadelphia
R15ES26370	Promotion of Pancreatic Cancer by Perfluorooctanoic Acid	Hocevar, Barbara A	Indiana University Bloomington
R15GM110632	Label-Free Nanopore Biosensor for Rapid, Ultra Sensitive, and Multiplex Detection of Protease Activities	Guan, Xiyun	Illinois Institute of Technology
R21AA26462	Mechanisms of Alcohol Initiation of Chronic Pancreatic Diseases	Logsdon, Craig D	The University of Texas MD Anderson Cancer Center
R21AI124687	Stromal IL-6/Jak-STAT Signaling and Pancreatitis	Ostrowski, Michael C (Contact); Lesinski, Gregory B	The Ohio State University
R21AR71021	Modeling Muscle Wasting in Cancer Cachexia	Guttridge, Denis C	The Ohio State University
R21CA175699	Pancreatic Cancer Control by A Novel Combination Treatment	Mackenzie, Gerardo Guillermo	The State University New York at Stony Brook
R21CA179362	A Creative Integration of Omega-3 Fatty Acids into Pancreatic Cancer Chemotherapy	Cui, Zhengrong	The University of Texas at Austin
R21CA181851	Improving Radiation Therapy for Pancreatic Cancer	Wang, Xinhui	Massachusetts General Hospital
R21CA182977	Multi-Tracer PET/CT Imaging of Gemcitabine Response in Pancreatic Cancer	Kadrmas, Dan J (Contact); Garrido-Laguna, Ignacio	The University of Utah

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R21CA185209	Two Phospho-Compounds for Pancreatic Cancer Prevention	Mackenzie, Gerardo Guillermo	The State University New York at Stony Brook
R21CA185276	A New Energy Restriction Mimetic that Targets Pancreatic Cancer	Lanza-Jacoby, Susan Patricia	Thomas Jefferson University
R21CA185689	Non-invasive Differentiation of Benign Lesions from Aggressive Pancreatic Cancer	Craik, Charles Scott (Contact); Kirkwood, Kimberly Saunders	University of California, San Francisco
R21CA185808	Genetic Testing for Men from Hereditary Cancer Families	Schwartz, Marc D	Georgetown University
R21CA185962	Pancreatic Cyst Fluid miRNome for Biomarkers of Pancreatic Cancer	Sen, Subrata	The University of Texas MD Anderson Cancer Center
R21CA186175	Targeting DCLK1 Kinase Activity in Pancreatic Cancer	Houchen, Courtney Wayne	The University of Oklahoma Health Sciences Center
R21CA186791	Needle Biopsy Preservation and Preparation for Rapid 3-D Pathology of Pancreas	Seibel, Eric J	University of Washington
R21CA187498	Development of D-Peptide Inhibitors of Oncogenic KRAS Mutants	Li, Yue Ming	Sloan-Kettering Institute
R21CA187869	Detection of 5-hmC as a Novel Screening Biomarker for Pancreatic Cancer	Zhang, Wei (Contact); Hou, Lifang	Northwestern University
R21CA188818	Targeting PAK4 for Overcoming Drug Resistance in Pancreatic Cancer	Azmi, Asfar Sohail (Contact); Mohammad, Ramzi M	Wayne State University
R21CA189775	Therapeutic Monitoring in Pancreatic Cancer Using an Exosome Based Mass Spec Assay	Lubman, David M	University of Michigan at Ann Arbor
R21CA191343	Defining the Role for a Lipid Kinase in the Progression of Pancreatic Cancer	Ling, Kun	Mayo Clinic, Rochester
R21CA191347	Discoidin Domain Receptors: Novel Players in Pancreatitis and Pancreatic Preneoplasia	Fridman, Rafael A (Contact); Crawford, Howard C	Wayne State University

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R21CA191392	Identifying New Drug Targets to Block K-Ras/Raf in Pancreatic Cancer	Stork, Philip J S	Oregon Health & Science University
R21CA191515	New Transgenic Animal Model to Study Pancreatic Cancer	Fisher, Paul B	Virginia Commonwealth University
R21CA191622	Preclinical Validation of U1 Adaptors for Suppression of KRAS in Pancreatic Cancer	Gunderson, Samuel I (Contact); Carpizo, Darren Richard	Rutgers, The State University of New Jersey
R21CA191631	Dual Recombinase Models of Pancreatic Cancer	Seeley, Elliott Scott	University of California, San Francisco
R21CA191715	AGX1/2 Inhibitors as Key Modulators of the Hexosamine Biosynthetic Pathway	Yarema, Kevin J	Johns Hopkins University
R21CA191923	Targeting PHD2 in Pancreatic Cancer	Han, Haiyong	Translational Genomics Research Institute
R21CA191956	TDG as a Novel Target to Enhance Gemcitabine Killing of Pancreatic Cancer Cells	Bellacosa, Alfonso (Contact); Yen, Timothy	Research Institute of Fox Chase Cancer Center
R21CA192629	Glycan Control of Stem Cell-Associated Pathways in Pancreatic Cancer	Bellis, Susan L	The University of Alabama at Birmingham
R21CA194745	High Fat Diet Stimulates Pancreatic Cancer through the Actions of Cholecystokinin	Smith, Jill P	Georgetown University
R21CA194764	Regulation of Pancreatic Ductal Adenocarcinoma Progression by Hnf4a	Snyder, Eric Lee	The University of Utah
R21CA194836	Mouse Model to Study Dependence of Pancreatic Cancer on Pik3ca for Progression	Lin, Richard Z	The State University of New York at Stony Brook
R21CA194839	A Novel Mouse Model to Identify Biomarkers of IPMN Formation and Progression	Sander, Maike	University of California, San Diego
R21CA194910	Somatic Engineering-based Models of Pancreatic Cancer	Winslow, Monte Meier	Stanford University
R21CA195694	Targeting Pancreatic Cancer with Novel Mnk-eIF4E and AR Modulating Agents	Njar, Vincent Collins Ofuka	University of Maryland Baltimore

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R21CA196485	High Specificity MicroRNA Microarray Analysis without PCR for Cancer Screening and Research	Saraf, Ravi F	University of Nebraska Lincoln
R21CA198109	Deciphering SIRT6-dependent Metabolic Liabilities in Pancreatic Cancer	Mostoslavsky, Raul	Massachusetts General Hospital
R21CA198265	New HuR Inhibitor Against Pancreatic Cancer EMT and CSCs	Chen, Qi	University of Kansas Medical Center
R21CA198287	Aptamers as Proteomic Tools for Pancreatic Cancer Biomarker Identification	White, Rebekah	Duke University
R21CA198292	IGF-II-Based Approach to Therapy for Pancreatic Cancer	MacDonald, Richard G	University of Nebraska Medical Center
R21CA198365	Dissecting ALK4 Function in Cancer Progression	Blobe, Gerard C	Duke University
R21CA199010	Treating Pancreatic Cancer with Listeria-32P	Gravekamp, Claudia	Albert Einstein College of Medicine
R21CA199050	Targeting Kras in Pancreatic Cancer	Ozpolat, Bulent (Contact); Lopez-Berestein, Gabriel ; Maitra, Anirban	The University of Texas MD Anderson Cancer Center
R21CA202487	KRAS Mutations in Plasma cfDNA as Predictor to Erolinib Response in Advanced Pancreatic Cancer	Li, Donghui (Contact); Overman, Michael J	The University of Texas MD Anderson Cancer Center
R21CA202745	Dim Light at Night Alters Pancreatic Cell Signaling and Predisposes to Pancreatic Adenocarcinoma	Nelson, Randy J	The Ohio State University
R21CA205094	Primers: Combining Radiotherapy and Immunotherapy Using Next Generation Radiotherapy Biomaterials	Ngwa, Wilfred	Dana–Farber Cancer Institute
R21CA205501	Developing Therapy for the Treatment of Cholangiocarcinoma	Yoon, Karina J	The University of Alabama at Birmingham
R21CA206013	(PQ1) Cellular Senescence as an Initiating Event in Malignant Transformation	David, Gregory	New York University School of Medicine

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R21CA207779	Detection and Histopathology Localization of O-Glycans and Glycosaminoglycans in Tissues	Drake, Richard R	Medical University of South Carolina
R21CA209366	Identifying Insulin Resistance Biomarkers and Metabolomic Signature as Predictors of Precursors to Pancreatic Cancer	Zhang, Jianjun (Contact); Schmidt, Christian Maximillian	Indiana University-Purdue University at Indianapolis
R21CA209536	Targeting Cytokine Mediated CREB Activation in Pancreatic Cancer	Nagathihalli, Nagaraj S	University of Miami School of Medicine
R21CA212827	Single-Molecule Mechanical Detection of Protein and MicroRNA Cancer Biomarkers	Wong, Wesley Philip	Boston Children's Hospital
R21CA213114	Reprogramming Tumor-Associated Macrophages in PDAC with MicroRNA Nano-Vectors	Amiji, Mansoor M (Contact); Mackenzie, Gerardo Guillermo; Matthaiolampakis, Georgios	Northeastern University
R21CA215860	CEST MRI Assessment of Tumor Vascular Permeability Using Non-Labeled Dextrans	Liu, Guanshu	Hugo W. Moser Research Institute Kennedy Krieger
R21CA216722	Novel Pan-Ralgef Inhibitors to Block Pancreatic Cancer.	Clark, Geoffrey J	University of Louisville
R21CA218495	Inhibition of Stromal-Derived DKK3 to Enhance the Response of Pancreatic Cancer to Immunotherapy	Hwang, Rosa F	The University of Texas MD Anderson Cancer Center
R21CA218732	PancFit: Do Angiogenic Biomarkers Correlate with Improved Progression Free Survival in Pancreatic Cancer?	Schadler, Keri L (Contact); Katz, Matthew H G; Ngo-Huang, An Thuy	The University of Texas MD Anderson Cancer Center
R21CA218960	Identification of Plasma- and Exosome-Based Protein Biomarkers for Early Detection of Pancreatic Cancer Using SOMAscan Technology	Libermann, Towia A	Beth Israel Deaconess Medical Center
R21CA218968	Novel Model to Study PDAC Using Normal Human Pancreatic Tissue	Wang, Pei	The University of Texas Health Science Center

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R21CA219899	PET Imaging of the Tumor Microenvironment for Cancer Detection	Wadas, Thaddeus J	Wake Forest University Health Sciences
R21CA220073	Predicting the Diagnosis of Pancreatic Cancer by Leveraging Big Data	Jeon, Christie Younghae	Cedars-Sinai Medical Center
R21CA220625	Targeting Hyaluronan Synthesis and Signaling with BET Inhibitors in Pancreatic Cancer	Kumar, Krishan	Northwestern University
R21CA223102	Co-targeting PDAC Tumor Cells and the Microenvironment to Succeed in EGFR/ErbB2-Targeted Therapy	Yu, Dihua	The University of Texas MD Anderson Cancer Center
R21CA223304	Accurate Determination of Dose to Mobile Organs at Risk in Hypofractionated Ablative Radiotherapy for Locally Advanced Pancreatic Cancer	Mageras, Gikas S	Sloan-Kettering Institute
R21CA223403	A Pre-Clinical X-Ray/Optical Tomography-Guided Radiation Research Platform for Pancreatic Cancer	Wang, Ken Kang-Hsin (Contact); Tran, Phuoc T	Johns Hopkins University
R21CA223429	New Strategy for Pancreatic Cancer Therapy	Solheim, Joyce C	University of Nebraska Medical Center
R21CA224280	3-D Biomimetic Image-Based Stromal Models of Pancreatic Cancer for Drug Screening	Campagnola, Paul J (Contact); Skala, Melissa Caroline	University of Wisconsin–Madison
R21CA230120	Deployable Endoluminal Ultrasound Phased Array for Precision Treatment of Pancreatic Cancer	Diederich, Chris John	University of California, San Francisco
R21CA231196	Taste Receptor Family 2 Member 9 as a Novel Target for Imaging Cancer Associated Fibroblasts in Pancreatic Cancer	Kelly, Kimberly A	University of Virginia
R21EB20737	Novel Platform to Achieve High Avidity of Heterodimers for Targeted Cancer Imaging	Zeng, Dexing	University of Pittsburgh at Pittsburgh

Project Number	Title	Principal investigator(s)	Institution
R21EB22770	High Sensitivity Molecular Ultrasound Imaging in Pancreatic Cancer	Willmann, Juergen Karl (Contact); Dahl, Jeremy	Stanford University
R21ES25839	Cytosolic Ah Receptor: Mechanism of Action	Safe, Stephen H	Texas A&M AgriLife Research
R21HG9010	An Integrated Microfluidics Platform for Rapid and Sensitive Exosome RNA	Chang, Hsueh-Chia (Contact); Go, David B; Hill, Reginald; Senapati, Satyajyoti	University of Notre Dame
R21LM12759	Identification and Characterization of Interaction Atlases in Human	Otu, Hasan	University of Nebraska Lincoln
R33CA183685	Advanced Methods to Evaluate Extracellular Matrix and Crosslinking in the Tumor M	Hansen, Kirk C (Contact); Weaver, Valerie Marie	University of Colorado Denver
R33CA204704	Multiplex FRET Imaging of Kinase-Epigenome Interregulations in Live Cancer Cells	Wang, Yingxiao	University of California, San Diego
R33CA206907	Rapid Unbiased Isolation and *In Situ* RNA Analysis of Circulating Tumor Cells Using a Magnetic Micropore-Based Diagnostic Chip	Issadore, David Aaron	University of Pennsylvania
R33CA206949	Advanced Development and Validation of 3 Dimensional Spheroid Culture of Primary Cancer Cells Using Nano3-D Technology	Spicer, Timothy Patrick	Scripps Florida
R33CA225248	Area A: In-Depth Proteome Mapping of the Tumor Microenvironment with Single-Cell Resolution	Kelly, Ryan T	Battelle Pacific Northwest Laboratories
R33CA225380	Molecular Beacon Based Extracellular mRNA and Protein Detection for Early Cancer Diagnosis	Lee, Ly James (Contact); Fleisher, Martin	The Ohio State University
R35CA197562	Mediators of Cancer Cell Homeostasis: Intervention Targets Common to Diverse Types of Cancer	Land, Hartmut	University of Rochester

Project Number	Title	Principal investigator(s)	Institution
R35CA197563	Reversing Cellular Immortality in Cancer	Artandi, Steven E	Stanford University
R35CA197566	Mechanisms Governing Metastatic Dormancy and Reactivation	Giancotti, Filippo G	The University of Texas MD Anderson Cancer Center
R35CA197591	Integrative Approaches to Elucidate p53 Transcriptional Networks During Carcinogenesis	Attardi, Laura D	Stanford University
R35CA197627	Breaking the Obesity-Cancer Link: New Targets and Strategies	Hursting, Stephen D	The University of North Carolina at Chapel Hill
R35CA197684	IKK/NF-kappa B Signaling in Cancer: Therapy, Resistance, and Tumor Initiating Cells	Baldwin, Albert Sidney	The University of North Carolina at Chapel Hill
R35CA197699	Molecular Strategies for Early Detection and Targeting of Cancer	Reya, Tannishtha	University of California, San Diego
R35CA197709	New Ways of Targeting K-Ras	McCormick, Frank Patrick	University of California, San Francisco
R35CA197731	Targeting Mutant KRAS for Cancer Therapy	Sebti, Said M	H. Lee Moffitt Cancer Center & Research Institute
R35CA209960	Molecular Imaging and Theranostics of Cancer	Bhujwalla, Zaver M	Johns Hopkins University
R35CA210039	Immunoprevention and Immunosurveillance of Human Non-Viral Cancers	Finn, Olivera J	University of Pittsburgh at Pittsburgh
R35CA210088	The Role of Stem Cells and the Microenvironment in Gastrointestinal Cancers	Wang, Timothy Cragin	Columbia University Health Sciences
R35CA210263	Oncogenic Ras-induced Macropinocytosis: A New Paradigm for Metabolic Adaptation	Bar-Sagi, Dafna	New York University School of Medicine
R35CA220508	Interrogating the Evolutionary Dynamics of Cancer for Clinical Benefit and Actionability	Iacobuzio-Donahue, Christine A	Sloan-Kettering Institute
R35CA231989	The MYC Transcription Factor Network and the Path to Cancer	Eisenman, Robert Neil	Fred Hutchinson Cancer Research Center

Project Number	Title	Principal investigator(s)	Institution
R35CA232113	Targeting Undruggable RAS for Cancer Treatment	Der, Channing J	The University of North Carolina at Chapel Hill
R35CA232124	Identifying Metabolic Dependencies of Pancreatic Cancers	Kimmelman, Alec	New York University School of Medicine
R37CA214679	Multi-site Gastrointestinal Cancer Detection by Stool DNA Methylation	Kisiel, John	Mayo Clinic Rochester
R37CA215427	Clinical Translation of Nuclear Export Inhibitor in Metastatic Pancreatic Cancer	Azmi, Asfar Sohail	Wayne State University
R37CA219697	IRAK4 as a Novel Immunotherapeutic Target in Pancreatic Ductal Adenocarcinoma	Lim, Kian H	Washington University
R37CA222215	Combined Radiation Acoustics and Ultrasound Imaging for Real-Time Guidance in Radiotherapy	El Naqa, Issam Mustafa	University of Michigan at Ann Arbor
R37CA227865	Targeting Pancreatic Cancers Metabolic Addiction to HuR	Winter, Jordan M	Case Western Reserve University
R37CA229417	Spacer Enabled Robust Radiation Therapy (SERRT)	Ding, Kai	Johns Hopkins University
R37CA230645	Stress-Adaptation in Obesity-Associated Pancreatic Cancer	Grabocka, Elda	Thomas Jefferson University
R41CA195947	Novel Immunotherapy Strategy for Treatment of Pancreatic Cancer	Mukherjee, Pinku	Oncotab, Inc.
R41CA203090	Pancreatic Ductal Adenocarcinoma Targeted Ultrasound Contrast Agent Development	Unger, Evan Charles (Contact); Willmann, Juergen Karl	Nuvox Pharma, LLC
R41CA213718	Ultrasensitive SERS Nano-Sensors for Pancreatic Cancer Diagnosis and Prognosis	Junker, Wade M (Contact); Kaur, Sukhwinder	Sanguine Diagnostics and Therapeutics
R41CA217482	Development of a Protein Drug for Pancreatic Cancer Treatment	Liu, Zhi-Ren	Proda Biotech, LLC
R41CA228695	Development of GPER Agonists as Cancer Therapeutics	Ridky, Todd W	Linnaeus Therapeutics, LLC

Project Number	Title	Principal investigator(s)	Institution
R43CA200052	Screening for Pancreatic Cancer via Nanocytology of Duodenal Cells	Cherkezyan, Lusik Surenovna (Contact); Subramanian, Hariharan	Nanocytomics, LLC
R43CA200398	Digital Analysis of Plasma miRNA Populations in Pancreatic Cancer	Metzker, Michael L	Redvault Biosciences, LP
R43CA203273	Plasma Generation of Aqueous Chemotherapeutic Solutions	Joslin, Jessica	Symbios Technologies, Inc.
R43CA206581	ERASE - A New Dual Thermal Ablation/SCN Device System for Treating Pancreatic Cancer	Van Buskirk, Robert G	Cell Preservation Services, Inc.
R43CA210854	A Highly Specific NIRF/PET Probe for the Detection of Cancer and Metastases	Yang, Xinlin	Imol Radiopharmaceuticals, LLC
R43CA213863	A Scalable Blood-based Pancreatic Cancer Test for High-Risk Screening	Freedman, David	Nanoview Diagnostics, Inc.
R43CA217400	First-in-Class TREM-1 Inhibitors in Combination Therapy for Pancreatic Cancer	Sigalov, Alexander B	Signablok, Inc.
R43CA217502	Oral Formulation for Novel Inhibitor of Ras Driven Cancers	Canzoneri, Joshua (Contact); Boyd, Michael R	Adt Pharmaceuticals, LLC
R43CA221400	Novel Monobody Therapy for Pancreatic Cancer	Yu, Bo (Contact); Larrick, James W	Larix Bioscience, LLC
R43CA221555	Novel Targeted Therapy for Pancreatic Cancer	Herrera, Victoria L	Abtelum Biomedical, Inc.
R43CA224739	Fluorescent Nanoparticles to Improve Resections of Microscopic Pancreatic Tumors	Colby, Aaron Henry	Ionic Pharmaceuticals
R43CA225169	Endoscopic Flexible Pancreatic Tumor Ablation System with Reduced Force Effector and Specialized Ablation Zone	Snook, Kevin A	Actuated Medical, Inc.
R43CA233401	Quantifiable Thermal Therapy Using Magnetic Resonance Thermometry Imaging	Floriano, Pierre	Neotherma Oncology, Inc.
R43CA236101	Molecular Beacons in Lipoplex Nanoparticles for Extracellular	Lee, Ly James (Contact); Kwak, Kwang Joo	Nanomaterial Innovation, Ltd

Project Number	Title	Principal investigator(s)	Institution
	Vesicles Based Cancer Diagnosis		
R43CA236164	Development of Targeted, Safe and Effective Drugs Against Pancreatic Ductal Adenocarcinoma (PDAC) by Leveraging a Novel, Comprehensive, Computational Drug Discovery Approach	Heuer, Timothy S	Twoxar, Inc.
R43DK107152	Novel Technologies for Improved Slide Quality of Pancreatic Fine-Needle Aspirates	Nair, Shrikumar Ambujakshan	Affinergy, LLC
R43DK115341	Development of Fluorogenic Substrates for the Diagnosis of Pancreatic Cysts	Winter, Michael B	Alaunus Biosciences, Inc.
R44CA174025	Development of Monoclonal Antibodies to Treat Pancreatic Cancer	Sureban, Sripathi M	Coare Biotechnology, Inc.
R44CA183265	FrostBite - A Unique Catheter for Endoscopic Cryoablation	Baust, J M	Cell Preservation Services, Inc.
R44CA199058	A Prognostic Blood Test to Monitor Pancreatic Cancer Treatment by MiRNA Profiling	Saraf, Ravi	Vajra Instruments, Inc.
R44CA200186	Molecular MR Imaging of the Desmoplastic Response in Pancreatic Cancer	Humblet, Valerie	Collagen Medical, LLC
R44CA203052	Laser Tissue Welding: Breaching Barriers in the Surgical Management of the Pancreas	Wadia, Yasmin (Contact); Barakat, Omar	Laser Tissue Welding, Inc.
R44CA203336	Immuno-Oncology for Pancreatic Cancer: A Combination Clinical Trial with Chemotherapy and Radiation	Aguilar-Cordova, Estuardo (Contact); Aguilar, Laura K	Advantagene, Inc.
R44CA206663	Novel MAP Kinase Pathway Inhibitors to Treat Pancreatic Ductal Adenocarcinoma	Slee, Deborah (Contact); Samatar, Ahmed	Kalyra Pharmaceuticals, Inc.
R44CA210770	Clinical Evaluation of the Novel, Uni-Directional, Pd-103 Civasheet for Pancreatic Cancers	Perez, Kristy	Civatech Oncology, Inc.

Project Number	Title	Principal investigator(s)	Institution
R44CA224460	Implantable Iontophoresis Chemotherapy Delivery Device for Direct Infusion of Gemcitabine into Pancreatic Adenocarcinoma: Device Development and First-In-Human Clinical Trial	Daunch, William	Advanced Chemotherapy Technologies, Inc.
R44CA224472	Development of a DCLK1 siRNA Nanoparticle as Targeted Therapy to Treat Pancreatic Cancer	Sureban, Sripathi M	Coare Holdings, Inc.
R44CA224619	Seromic Mucin Signature for the Early Diagnosis of Pancreatic Cancer	Junker, Wade M (Contact); Kaur, Sukhwinder	Sanguine Diagnostics and Therapeutics
R44CA224994	Ultra-High Content Analysis (UHCA) of Single Cells in Tissue: 60+ Channel Immunofluorescence Labeling Kits and Companion Imaging Software for Everyone	Nederlof, Michel	Quantitative Imaging Systems, LLC
R44CA233157	Selection and Preclinical Development of a Bacteria-Targeting, Non-Antibiotic Lead Candidate to Improve Cancer Chemotherapy Outcomes	Peterson, Ward	Symberix, Inc.
R44DK117472	MUC4/16 Assay for the Early Diagnosis and Management of Benign and Malignant Pancreatic Diseases	Junker, Wade M (Contact); Jain, Maneesh ; Sasson, Aaron R	Sanguine Diagnostics and Therapeutics
R50CA211425	Defining and Targeting Mechanisms of Pancreas Cancer Pathogenesis	Whittle, Martin	Fred Hutchinson Cancer Research Center
R50CA211437	Revealing Cancer Metabolism via Mass Spectrometry and Isotope Tracers	Lu, Wenyun	Princeton University
R50CA211462	Critical Resources Provided by UNMC RAP Biorepository Stimulate Cancer Research	Grandgenett, Paul M	University of Nebraska Medical Center
R50CA211506	Preclinical Models for Cancer Therapeutic Development	Park, Youngkyu	Cold Spring Harbor Laboratory
R50CA232985	Targeting the Immunosuppressive Tumor	Zhang, Yaqing	University of Michigan at Ann Arbor

Project Number	Title	Principal investigator(s)	Institution
	Microenvironment in Pancreatic Cancer		
R50CA233186	The Role of DCLK1 in the Initiation of Pancreatic Ductal Adenocarcinoma and Colorectal Cancer	Qu, Dongfeng	The University of Oklahoma Health Sciences Center
S10OD25190	6 MeV/amu Ion Linac for Deep-Penetration Microbeam and Millimeter-Beam Charged-Particle Irradiations in Small Animals and Biological Tissues	Brenner, David Jonathan	Columbia University Health Sciences
U01CA128454	Discovery and Development of Cancer Glycomarkers	Pierce, J Michael	University of Georgia
U01CA152653	Detection and Prognosis of Early Stage Pancreatic Cancer by Interdependent Plasma Markers	Haab, Brian B (Contact); Allen, Peter J; Brand, Randall	Van Andel Research Institute
U01CA168896	Targeted Glycomics and Affinity Reagents for Cancer Biomarker Development	Haab, Brian B	Van Andel Research Institute
U01CA175315	MicroRNA-1291 in Regulation of Xenobiotic Disposition and Cell Differentiation	Yu, Aiming	University of California, Davis
U01CA176058	The Dana–Farber Cancer Institute Cancer Target Discovery and Development Center	Hahn, William C (Contact); Golub, Todd R	Dana–Farber Cancer Institute
U01CA176303	An Integrated Computational and Functional Genomics Discovery Engine for Preclinical	Kemp, Christopher J	Fred Hutchinson Cancer Research Center
U01CA178960	Targeting Pancreatic Cancer Energy Metabolism, Tumor Growth, and Metastasis	Dwinell, Michael B (Contact); Kalyanaraman, Balaraman	Medical College of Wisconsin
U01CA187508	A Prospective Investigation of the Oral Microbiome and Pancreatic Cancer	Palmer, Julie R (Contact); Shu, Xiao-Ou	Boston University Medical Campus
U01CA196403	Imaging and Molecular Correlates of Progression in Cystic Neoplasms of the Pancreas	Maitra, Anirban	The University of Texas MD Anderson Cancer Center

Project Number	Title	Principal investigator(s)	Institution
U01CA198846	UCLA Multifunctional Mesoporous Silica Nanoparticle Platform for Treatment of Pancreas Cancer	Nel, Andre Elias (Contact); Donahue, Timothy R; Meng, Huan; Zink, Jeffrey I	University of California, Los Angeles
U01CA198913	Stroma Breaking Theranostic Nanoparticle for Targeted Pancreatic Cancer Therapy	Yang, Lily (Contact); Mao, Hui	Emory University
U01CA199235	Identification of Synthetic Lethal Interactors in Pancreatic Cancer	Der, Channing J (Contact); Cox, Adrienne D	The University of North Carolina at Chapel Hill
U01CA199253	Systematic Identification of Oncogenic KRAS Synthetic Lethal Interactions	Hahn, William C	Broad Institute
U01CA200466	Validation of Biomarkers for Early Diagnosis and Risk Prediction of Pancreatic Neoplasms	Brand, Randall (Contact); Batra, Surinder K	University of Pittsburgh at Pittsburgh
U01CA200468	A Clinical Validation Center for Early Detection of Pancreatic Cancer	Maitra, Anirban	The University of Texas MD Anderson Cancer Center
U01CA202241	ECM Geometrical and Mechanical Properties Modulate RTK Signaling	Groves, Jay T (Contact); Weaver, Valerie Marie	University of California, Berkeley
U01CA210020	Molecular Imaging Methods for the Detection of Pancreatic Ductal Adenocarcinoma	Iagaru, Andrei (Contact); Park, Walter Gwang-Up	Stanford University
U01CA210138	Mayo Clinic Prospective Resource for Biomarker Validation and Early Detection of Pancreatic Cancer	Petersen, Gloria M (Contact); Zaret, Kenneth S	Mayo Clinic, Rochester
U01CA210170	Using Markers to Improve Pancreatic Cancer Screening and Surveillance	Goggins, Michael G	Johns Hopkins University
U01CA210171	Circulating Biomarker Consortium for Pancreatic Cancer Early Detection	Wolpin, Brian Matthew	Dana–Farber Cancer Institute
U01CA210240	Pancreatic Cancer Detection Consortium	Hollingsworth, Michael A	University of Nebraska Medical Center
U01CA213862	Nanovaccine Platforms to Combat Pancreatic Cancer	Narasimhan, Balaji (Contact); Jain, Maneesh; Salem, Aliasger K	The Iowa State University

Project Number	Title	Principal investigator(s)	Institution
U01CA214254	Noncoding RNA Biomarkers for Noninvasive and Early Detection of Pancreatic Cancer	Goel, Ajay (Contact); Von Hoff, Daniel D	Baylor Research Institute
U01CA214263	Circulating Biomarkers and Imaging for Early Detection of Pancreatic Cancer	Sen, Subrata (Contact); Killary, Ann M	The University of Texas MD Anderson Cancer Center
U01CA216449	Sensitization to Chemoradiation by Therapeutic Targeting of the DNA Damage Response	Lawrence, Theodore S	University of Michigan at Ann Arbor
U01CA216468	Enhancing Chemoradiation Efficacy Through Unbiased Drug Discovery Approaches	Lin, Steven Hsesheng (Contact); Krishnan, Sunil	The University of Texas MD Anderson Cancer Center
U01CA217665	Peptide-based Targeted Molecular Imaging for Early Detection in Pancreatic Cancer	Sutcliffe, Julie L	University of California, Davis
U01CA217842	Integrative Bioinformatics and Functional Characterization of Oncogenic Driver Aberrations in Cancer	Mills, Gordon B (Contact); Scott, Kenneth L	The University of Texas MD Anderson Cancer Center
U01CA221046	Pretargeted Clinical Imaging of CA19.9 in Pancreatic Cancer	Lewis, Jason S (Contact); Zeglis, Brian Matthew	Sloan-Kettering Institute
U01CA224013	CSHL-JAX Patient-Derived Models of Pancreatic Cancer as Systems for Investigating Tumor Heterogeneity	Tuveson, David A (Contact); Robson, Paul	Cold Spring Harbor Laboratory
U01CA224145	Interrupting Cellular Crosstalk in the Immunosuppressive Microenvironment of Pancreas Cancer	Crawford, Howard C (Contact); Pasca Di Magliano, Marina	University of Michigan at Ann Arbor
U01CA224146	Systematic Interrogation of the Pancreatic Cancer Microenvironment in Patient-Derived Specimens	Hahn, William C	Dana–Farber Cancer Inst
U01CA224175	Defining neoantigen immunodominance for antigen selection and biomarker discovery in human pancreatic cancer immunotherapy	Balachandran, Vinod P (Contact); Leach, Steven D	Sloan-Kettering Institute
U01CA224193	Disrupting the Immune and Drug-Privileged	Hingorani, Sunil R	Fred Hutchinson Cancer Research Center

Project Number	Title	Principal investigator(s)	Institution
	Microenvironment in Pancreas Cancer		
U01CA224348	Reprogramming PDAC Tumor Microenvironment to Improve Immunotherapy	Jain, Rakesh K (Contact); Pittet, Mikael	Massachusetts General Hospital
U01CA233581	Sialylation-dependent Mechanisms Driving Pancreatic Cancer Progression	Bellis, Susan L (Contact); Wells, Lance	The University of Alabama at Birmingham
U01DK108288	The Exocrine and Endocrine Pancreas in Type 2 Diabetes, Pancreatitis and Cancer	Chari, Suresh T (Contact); Topazian, Mark D	Mayo Clinic, Rochester
U01DK108300	A Clinical Center to Study Immunological and Hormonal Biomarkers for the Diagnosis, Prediction and Treatment of Chronic Pancreatitis and Its Associated Development to Diabetes and Pancreas Cancer	Park, Walter Gwang-Up (Contact); Habtezion, Aida; Kim, Seung K	Stanford University
U01DK108306	Consortium for the Study of Pancreatitis: Pittsburgh Clinical Center	Yadav, Dhiraj (Contact); Whitcomb, David Clement	University of Pittsburgh at Pittsburgh
U01DK108314	Pathophysiology, Epidemiology, and Prevention of Pancreatogenic Diabetes	Pandol, Stephen J (Contact); Goodarzi, Mark	Cedars-Sinai Medical Center
U01DK108320	U01Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Clinical Centers	Forsmark, Christopher E (Contact); Cusi, Kenneth; Hughes, Steven J	University of Florida
U01DK108323	Indiana University Clinical Center for Chronic Pancreatitis Clinical Research Network	Fogel, Evan	Indiana University-Purdue University at Indianapolis
U01DK108326	Altered Microbiome in Pancreatitis, Diabetes and Pancreatic Cancer	Fisher, William E	Baylor College of Medicine
U01DK108327	The Ohio State University Pancreatic Disorders Network (OSU-PDN)	Conwell, Darwin Lewis (Contact); Banks, Peter Alan; Bellin, Melena D; Gariepy, Cheryl E; Gress, Francis G; Hart, Philip A;	The Ohio State University

Project Number	Title	Principal investigator(s)	Institution
		Palermo, Joseph; Steen, Hanno ; Topazian, Mark D; Whitcomb, David Clement	
U01DK108328	Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer: Coordinating and Data Management Center (CSCPDPC-CDMC)	Feng, Ziding (Contact); Maitra, Anirban	The University of Texas MD Anderson Cancer Center
U01DK108332	Chronic Pancreatitis, Diabetes and Pancreatic Cancer: A Prospective Approach	Van Den Eeden, Stephen K	Kaiser Foundation Research Institute
U01HL143365	Biomarkers and Mechanisms in Cancer Associated Thrombosis	Zwicker, Jeffrey (Contact); Chaikof, Elliot; Flaumenhaft, Robert C	Beth Israel Deaconess Medical Center
U01HL143403	Targeting the Plasminogen Activation System to Limit Pancreatic Cancer Progression and Associated Thrombosis	Flick, Matthew J (Contact); Fishel, Melissa L; Han, Bumsoo ; Wolberg, Alisa S	Cincinnati Children's Hospital Medical Center
U24CA209996	Building Protected Data Sharing Networks to Advance Cancer Risk Assessment and Treatment	Foster, Ian	The University of Chicago
U24CA210986	Center of Excellence for High Throughput Proteogenomic Characterization	Carr, Steven A (Contact); Gillette, Michael A	Broad Institute
U24CA224020	Pancreatic Ductal Adenocarcinoma Translational Resource Center (PATReC)	Wistuba, Ignacio I (Contact); Maitra, Anirban	The University of Texas MD Anderson Cancer Center
U24CA231858	Penn Quantitative MRI Resource for Pancreatic Cancer	Zhou, Rong (Contact); Odwyer, Peter J; Rosen, Mark Alan	University of Pennsylvania
U2CCA233284	Transition to Metastatic State: Lung Cancer, Pancreatic Cancer and Brain Metastasis	Pe'er, Dana (Contact); Iacobuzio-Donahue, Christine A	Sloan Kettering Institute
U2CCA233303	Washington University Human Tumor Atlas Research Center	Ding, Li (Contact); Achilefu, Samuel;	Washington University

Project Number	Title	Principal investigator(s)	Institution
		Fields, Ryan C; Gillanders, William E	
U54CA210181	Center for Immunotherapeutic Transport Oncophysics	Ferrari, Mauro	Methodist Hospital Research Institute
U54CA210190	Center for Modeling Tumor Cell Migration Mechanics	Odde, David J (Contact); Largaespada, David Andrew; Rosenfeld, Steven S	University of Minnesota
U54CA217377	Quantitative and Functional Characterization of Therapeutic Resistance in Cancer	Manalis, Scott R (Contact); Lauffenburger, Douglas A	Massachusetts Institute of Technology
U54CA224065	The University of Texas PDX Development and Trial Center	Roth, Jack (Contact); Meric-Bernstam, Funda	The University of Texas MD Anderson Cancer Center
U54CA224083	Washington University PDX Development and Trial Center	Govindan, Ramaswamy (Contact); Ding, Li; Li, Shunqiang	Washington University
U54CA233396	1/3 Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center	Reams, Romonia Renee (Contact); Carpten, John D; Odedina, Folakemi T; Redda, Kinfe Ken; Stern, Mariana C; Wilkie, Diana J	Florida Agricultural and Mechanical University
U54CA233444	2/3 Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center	Odedina, Folakemi T (Contact); Carpten, John D; Reams, Romonia Renee; Redda, Kinfe Ken; Stern, Mariana C; Wilkie, Diana J	University of Florida
U54CA233465	3/3 Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center	Carpten, John D (Contact); Odedina, Folakemi T; Reams, Romonia Renee; Redda, Kinfe Ken; Stern, Mariana C; Wilkie, Diana J	University of Southern California

Project Number	Title	Principal investigator(s)	Institution
UH2CA191284	Leveraging GxE Interaction to Understand Pancreatic Cancer and Altered Metabolism	Kraft, Peter	Harvard T.H. Chan School of Public Health
UM1CA183727	Tennessee Valley Cooperative Human Tissue Network	Washington, Mary Kay	Vanderbilt University
UM1HG9426	Center for Functional Validation and Evaluation of ENCODE Enhancer Regions	White, Kevin P	The University of Chicago
ZIABC10298	Growth Regulation Section	Pastan, Ira	National Cancer Institute
ZIABC10774	T Cell Alternative p38 Activation Pathway	Ashwell, Jonathan	National Cancer Institute
ZIABC11185	Role of Immune and Inflammation Mediators in Progression of Pancreatic Cancer	Hussain, Syed	National Cancer Institute
ZIABC11267	Preclinical Drug Development in Pancreatic Cancer	Rudloff, Udo	National Cancer Institute
ZIABC11739	Development and Preclinical Application of Pancreatic Adenocarcinoma Models	Sharan, Shyam	National Cancer Institute

FY 2016, 2017, and 2018 NIH Projects Related to Small Cell Lung Cancer (SCLC)

Project Number	Title	Principal Investigator(s)	Institution
F30CA232475	Role of MYC Family Members in Driving Chemoresistance in Small Cell Lung Cancer	Grunblatt, Eli	University of Washington
F31CA206346	Investigating the Role of the Mek5-Erk5 Kinase Module in Small Cell Lung Cancer	Cristea, Sandra	Stanford University
F31CA225119	Elucidating and Targeting EZH2 in the DNA Damage Response in Small Cell Lung Cancer	Koyen, Allyson	Emory University

Project Number	Title	Principal Investigator(s)	Institution
F99CA223015	Identifying Genetic Drivers of the Immunosuppressive Tumor Microenvironment in Lung Cancer	Mollaoglu, Gurkan	The University of Utah
F99CA234942	Understanding Metabolic Vulnerabilities in Cancer and the Impact the Tumor Microenvironment Has on Cancer Progression	Russell, Shonagh	University of South Florida
K08CA222657	New Therapeutic Targets in Small Cell Lung Cancer that Are Epistatic or Synthetic Lethal with pRB Loss	Oser, Matthew Gilbert	Dana–Farber Cancer Institute
K08HL129081	Genetic and Molecular Dissection of Pulmonary Neuroendocrine (NE) Cell Development	Kuo, Christin Sucheng	Stanford University
K99CA201618	Investigation and Targeting of the Transcriptional and Epigenetic Landscape of Small Cell Lung Cancer	Christensen, Camilla L	Dana–Farber Cancer Institute
P30CA043703 (8085)	Developmental Therapeutics Research Program	Letterio, John James	Case Western Reserve University
R01CA112557	Molecular Mechanisms of Nickel-induced Tumorigenicity.	Huang, Chuanshu	New York University School of Medicine
R01CA136534	Structure-based Anti-Cancer Drug Development	Deng, Xing Ming	Emory University
R01CA181449	Interrogation of MLL2 as a Tumor Suppressor Gene in Lung Cancer	MacPherson, David	Fred Hutchinson Cancer Research Center

Project Number	Title	Principal Investigator(s)	Institution
R01CA194461	(PQ4A) Metabolic Plasticity of Pre-Malignant Cells During Tumor Progression	Park, Kwon-Sik	University of Virginia
R01CA194470	(PQB4) Stochastic Profiling of Functional Single-Cell States Within Solid Tumors	Janes, Kevin A	University of Virginia
R01CA197936	Determinants of Acquired Resistance in Small Cell Lung Cancer	Rudin, Charles M	Sloan Kettering Institute
R01CA200547	Investigating CREBBP as a Tumor Suppressor in Small Cell Lung Cancer	MacPherson, David	Fred Hutchinson Cancer Research Center
R01CA200905	Modulation of BAK in Lung Cancer Therapeutics	Deng, Xing Ming	Emory University
R01CA201513	Notch Signaling in Small Cell Lung Carcinoma	Sage, Julien	Stanford University
R01CA202956	Optimizing Treatment of Lung Cancer Patients with Comorbidities	Wisnivesky, Juan P (Contact); Kong, Chung	Icahn School of Medicine at Mount Sinai
R01CA206540	Molecular and Cellular Mechanisms of SCLC Metastasis	Sage, Julien	Stanford University
R01CA207295	Therapeutic Strategies for Targeting PARP1 in Small Cell Lung Cancer	Byers, Lauren Averett	The University of Texas MD Anderson Cancer Center
R01CA211095	Role of KDM5A in pRB-Mediated Differentiation	Benevolenskaya, Elizaveta V	University of Illinois at Chicago
R01CA213448	Immuno-PET Imaging of High-Grade Neuroendocrine Lung Tumors Using 89Zr-rovalpituzumab, a DLL3-targeting Monoclonal Antibody	Poirier, John Thomas (Contact); Lewis, Jason S; Rudin, Charles M; Weber, Wolfgang	Sloan Kettering Institute

Project Number	Title	Principal Investigator(s)	Institution
R01CA218545	Novel Approach to Attenuate Small Cell Lung Cancer Growth and Metastasis	Nasser, Mohd Wasim	University of Nebraska Medical Center
R01HL115207	The Lineage and Function of Neuroendocrine Cells in Lung Homeostasis and Injury	Chuang, Pao-Tien	University of California, San Francisco
R03CA195253	Genomic and Transcriptomic Characterization of Atypical Carcinoids of the Lung	McKay, James Dowling	International Agency for Research on Cancer
R03CA215777	Engineered Precancerous Cells and Tissues for Discovery of Lung Cancer Drivers	Park, Kwon-Sik	University of Virginia
R15CA161491	Capsaicin and Small Cell Lung Cancer Therapy	Dasgupta, Piyali	Marshall University
R21CA195110	Novel Protein Risk Markers for Lung Cancer	Perera, Frederica P	Columbia University Health Sciences
R21CA205340	Identifying Mechanisms of p53 and Rb Tumor Suppression in Small Cell Lung Cancer	Feldser, David	University of Pennsylvania
R21CA209121	Kinase Dependent Chemotherapy Resistance Mechanisms in Small Cell Lung Cancer	Kern, Jeffrey A	National Jewish Health
R21CA216504	Identifying Therapeutic Vulnerabilities of c-MYC-Driven Small Cell Lung Cancer	Oliver, Trudy Gale	The University of Utah
R21CA218778	Discovery of Predictive Biomarkers for Cancer Therapies Using Synthetic Lethality	Sinha, Subarna (Contact); Sambucetti, Lidia C	SRI International
R21CA218787	Applying Chemical Biology to Target	Haura, Eric B	H. Lee Moffitt Cancer Center and Research Institute

Project Number	Title	Principal Investigator(s)	Institution
	Deubiquitinating Enzymes in Lung Cancer		
R21CA226322	Identification and Targeting of Chemotherapy Refractory Small Cell Lung Cancer	Dowlati, Afshin	Case Western Reserve University
R35CA210068	New Paradigms for Targeting Truncal Driver Mutations	Kaelin, William G	Dana–Farber Cancer Institute
R43CA217394	Novel Targeted Therapeutic for Advanced Metastatic Disease	Yu, Bo (Contact); Larrick, James W	Larix Bioscience, LLC
U01CA176284	Lung Cancer Oncogenotype-Selective Drug Target Discovery	Roth, Michael G (Contact); Macmillan, John B; Minna, John D; White, Michael A	UT Southwestern Medical Center
U01CA209414	The Boston Lung Cancer Survival Cohort	Christiani, David C	Harvard T.H. Chan School of Public Health
U01CA213273	Novel Therapeutic Approaches for Enhancing Anti-Tumor Immunity in SCLC	Heymach, John V (Contact); Byers, Lauren Averett; Sage, Julien	The University of Texas MD Anderson Cancer Center
U01CA213285	Development of Risk and Early Detection Biomarker for Small Cell Lung Cancer	Hanash, Samir M	The University of Texas MD Anderson Cancer Center
U01CA213330	Extracellular Vesicles in Small Cell Lung Cancer Early Detection	Nana-Sinkam, Serge P (Contact); Lee, Ly James	Virginia Commonwealth University
U01CA213333	Targeting the Transcriptional and Epigenetic Landscape in Chemo-Refractory Small-Cell Lung Cancer	Wong, Kwok Kin (Contact); Gray, Nathanael Schiander	New York University School of Medicine
U01CA213338	Developing ASCL1 and NeuroD1 Lineage Oncogene Targeted	Minna, John D	UT Southwestern Medical Center

Project Number	Title	Principal Investigator(s)	Institution
	Therapy for Small Cell Lung Cancer		
U01CA213359	Preclinical Development of a DLL3-Targeted Theranostic for Small Cell Lung Cancer	Poirier, John Thomas	Sloan Kettering Institute
U01CA215845	Phenotype Transitions in Small Cell Lung Cancer	Quaranta, Vito (Contact); Lopez, Carlos Federico	Vanderbilt University
U01CA220323	Using Patient-Derived Models to Understand Drug Responses in SCLC	Dyson, Nicholas J (Contact); Farago, Anna Flora	Massachusetts General Hospital
U01CA224276	Phenotype Interactions in SCLC Development and Detection	Weaver, Alissa M (Contact); Lovly, Christine M; Sage, Julien	Vanderbilt University
U01CA224293	Targeting BCAT1 and Branched-Chain Amino Acid Metabolism for the Detection and Prevention of SCLC	Park, Kwon-Sik	University of Virginia
U01CA224326	Studies of the Initiation and Progression of Small Cell Lung Cancer Using Cells Derived by Differentiation from Human Pluripotent Stem Cells	Varmus, Harold E	Weill Medical College of Cornell University
U01CA231776	Bioinformatic-Chemical Approach to Credential Molecular Targets to Combat Rapid Chemo-Radiation Resistance in SCLC	Marchionni, Luigi (Contact); Hann, Christine L; Tran, Phuoc T	Johns Hopkins University
U01CA231844	Genomic and Functional Identification of Chemotherapy Resistance Mechanisms	Govindan, Ramaswamy (Contact); Griffith, Obi L; Oliver, Trudy Gale	Washington University

Project Number	Title	Principal Investigator(s)	Institution
	in Small Cell Lung Cancer		
U01CA231851	Molecular Mechanisms of SCLC Initiation and Detection in Mice and Humans	Krasnow, Mark A	Stanford University
U01CA233074	Targeting Alternative Splicing for TCR Discovery in Small Cell Carcinomas	Witte, Owen N (Contact); Crooks, Gay M; Xing, Yi	University of California, Los Angeles
U24CA213274	Coordinating Center for the NCI Small Cell Lung Cancer Research Consortium	Rudin, Charles M	Sloan Kettering Institute
U2CCA233284 (8209)	Biospecimen Acquisition, Processing and Classification Unit	Iacobuzio-Donahue, Christine A	Sloan Kettering Institute
U54CA217450	Phenotype Heterogeneity and Dynamics in SCLC	Quaranta, Vito	Vanderbilt University
ZIABC011418	Modulating Cancer Stem Cell Signaling in Thoracic Malignancies	Schrump, David	National Cancer Institute
ZIABC011492	Biomarkers in Cancer Diagnosis, Prognosis and Therapeutic Outcome	Harris, Curtis	National Cancer Institute
ZIDBC011540	Thoracic and Gastrointestinal Malignancies Branch Clinical Core	Hassan, Raffit	National Cancer Institute
ZIABC011672	Clinical Protocols in the Cancer Signaling Networks Section	Guha, Udayan	National Cancer Institute
ZIABC011787	Predictive Biomarker of BET Bromodomain Inhibitor in Small Cell Lung Cancer	Chen, Haobin	National Cancer Institute

Project Number	Title	Principal Investigator(s)	Institution
ZIABC011793	Exploiting DNA Replicative Stress for Novel Small Cell Lung Cancer Therapies	Thomas, Anish	National Cancer Institute
ZICBC011820	DNA Methylation Data Development for Small Cell Lung Cancer	Reinhold, William	National Cancer Institute
ZIABC011839	Developing an Effective BET Bromodomain Inhibitor Drug Combo to Target SCLC	Chen, Haobin	National Cancer Institute
261201500070C-5-0-1	Small Business Innovation Research Program (SBIR)	Crosswell, Hal	Kiyatec, Inc.
261201500070C-0-0-1	IGF::OT::IGF Small Business Innovation Research Program (SBIR)	Crosswell, Hal	Kiyatec, Inc.

Appendix I:
Funding for Chronic Diseases and Organ Systems

More information on NIH Categorical Spending is available at:
http://report.nih.gov/categorical_spending.aspx.

The amounts cited for Auditory System; Endocrine System; Immune System; Integumentary System; Kidney and Urologic Diseases; Musculoskeletal System; Skeletal Muscle; Skeletal System; Joint, Ligaments, and Connective Tissues; and Reproductive System are not designated as official NIH Research, Condition, and Disease Categories (RCDCs), because the figures were not compiled using the standard RCDC reporting method. As a result, these unofficial categories are not listed on the NIH RePORT website. These entries are marked with an asterisk (*).

Research Area (Dollars in Millions)	FY 2016	FY 2017	FY 2018
Auditory System*	$269	$288	$307
Otitis Media	$16	$9	$10
Brain Disorders	$4,577	$5,156	$5,882
ALS	$52	$78	$83
Alzheimer's Disease	$929	1,361	$1,789
Aphasia	$30	$34	$33
Autism	$232	$245	$281
Batten Disease	$5	$5	$7
Brain Cancer	$310	$332	$360
Cerebral Palsy	$26	$26	$26
Epilepsy	$153	$154	$184
Frontotemporal Dementia	$65	$91	$94
Pick's Disease	$8	$8	$8
Huntington's Disease	$37	$47	$52
Injury - Traumatic Brain Injury	$105	$116	$133
Intellectual and Developmental Disabilities	$418	$455	$515

Research Area (Dollars in Millions)	FY 2016	FY 2017	FY 2018
Autism	$232	$245	$281
Down Syndrome	$27	$35	$60
Fragile X Syndrome	$44	$46	$38
Fetal Alcohol Syndrome	$29	$28	$34
Multiple Sclerosis	$97	$111	$112
Parkinson's Disease	$161	$168	$193
Rett Syndrome	$14	$15	$16
Reye's Syndrome	$0	$0	$0
Schizophrenia	$254	$243	$248
Tourette Syndrome	$5	$6	$10
Tuberous Sclerosis	$26	$21	$23
Cancer	$5,589	$5,980	$6,335
Brain Cancer	$310	$332	$360
Breast Cancer	$656	$689	$721
Cervical Cancer	$99	$114	$112
Childhood Leukemia	$151	$177	$197
Colorectal Cancer	$274	$270	$314
HPV and/or Cervical Cancer Vaccine	$38	$59	$37
Liver Cancer	$83	$90	$113
Lung Cancer	$331	$352	$403
Lymphoma	$264	$266	$298
Hodgkin's Disease	$15	$12	$14
Neuroblastoma	$37	$53	$52
Ovarian Cancer	$144	$151	$159
Pancreatic Cancer	$168	$199	$215
Prostate Cancer	$253	$239	$261
Uterine Cancer	$50	$45	$47
Cardiovascular	$2,108	$2,197	$2,269

Research Area (Dollars in Millions)	FY 2016	FY 2017	FY 2018
Atherosclerosis	$385	$426	$417
Heart Disease	$1,289	$1,370	$1,403
Coronary Heart Disease	$419	$444	$444
Hypertension	$224	$235	$260
Chronic Fatigue Syndrome	$8	$15	$14
Dental/Oral and Craniofacial Disease	$518	$541	$575
Temporomandibular Muscle/Joint Disorder	$15	$13	$14
Diabetes	$1,084	$1,108	$1,039
Digestive Diseases	$1,745	$1,881	$2,242
Digestive Diseases (Gallbladder)	$11	$12	$17
Digestive Diseases (Peptic Ulcer)	$9	$8	$8
Inflammatory Bowel Disease	$126	$134	$144
Crohn's Disease	$64	$67	$69
Colorectal Cancer	$274	$270	$314
Liver Diseases	$635	$691	$802
Chronic Liver Disease and Cirrhosis	$293	$285	$324
Liver Cancer	$83	$90	$113
Hepatitis	$267	$306	$349
Hepatitis A	$3	$4	$5
Hepatitis B	$47	$42	$55
Hepatitis C	$107	$114	$129
Endocrine System*	$1,950	$2,059	$1,535
Estrogen	$205	$220	$230
Diethylstilbestrol	$1	$4	$9
Eye Disease and Disorders of Vision	$847	$882	$963
Macular Degeneration	$99	$100	$105
Hematology	$1,317	$1,385	$1,464

Research Area (Dollars in Millions)	FY 2016	FY 2017	FY 2018
Childhood Leukemia	$151	$177	$197
Cooley's Anemia	$18	$18	$18
Sepsis[1]	$116	$125	$135
Sickle Cell Disease	$92	$109	$104
Immune System*	$5,466	$7,609	$8,009
Allergic Rhinitis (Hay Fever)	$7	$6	$5
Asthma	$266	$286	$304
Autoimmune Disease	$883	$934	$888
Inflammatory Bowel Disease	$126	$134	$144
Lupus	$97	$109	$123
Multiple Sclerosis	$97	$111	$112
Myasthenia Gravis	$5	$5	$4
Psoriasis	$18	$17	$15
Scleroderma	$18	$17	$23
Childhood Leukemia	$151	$177	$197
Food Allergies	$76	$79	$59
Lymphoma	$264	$266	$298
Hodgkin's Disease	$15	$12	$14
Vaccine Related	$1,773	$1,823	$2,022
HPV and/or Cervical Cancer Vaccine	$38	$59	$37
Malaria Vaccine	$47	$61	$57
Vaccine Related (AIDS)	$605	$562	$562
Tuberculosis Vaccine	$27	$29	$40
Integumentary System*	$491	$525	$561
Psoriasis	$18	$17	$15
Scleroderma	$18	$17	$23
Kidney and Urologic Diseases*	$1,081	$1,108	$1,138

[1] Name revised in FY 2018 from Septicemia.

Kidney Disease	$574	$592	$598
Polycystic Kidney Disease	$26	$29	$31
Urologic Diseases	$506	$515	$541
Interstitial Cystitis	$9	$10	$13
Prostate Cancer	$253	$239	$261
Lung	$1,604	$1,718	$1,849
Acute Respiratory Distress Syndrome	$103	$107	$123
Asthma	$266	$286	$304
Chronic Obstructive Pulmonary Disease	$97	$100	$111
Cystic Fibrosis	$89	$91	$83
Emphysema	$29	$27	$28
Lung Cancer	$331	$352	$403
Perinatal/Neonatal Respiratory Distress Syndrome	$52	$62	$62
Pneumonia	$127	$114	$134
Mental Health	$2,454	$2,717	$3,010
Autism	$232	$245	$281
Attention Deficit Disorder	$47	$54	$58
Depression	$410	$438	$500
Schizophrenia	$254	$243	$248
Musculoskeletal System*	$1,217	$1,269	$1,372
Skeletal Muscle*	$453	$493	$527
Muscular Dystrophy	$79	$81	$81
Myotonic Dystrophy	$9	$11	$13
Duchenne/Becker Muscular Dystrophy	$33	$30	$32
Facioscapulohumeral Muscular Dystrophy	$9	$11	$11
Myasthenia Gravis	$5	$5	$4
Spinal Muscular Atrophy	$10	$11	$12
Skeletal System*	$523	$574	$628

Research Area (Dollars in Millions)	FY 2016	FY 2017	FY 2018
Osteogenesis Imperfecta	$16	$13	$12
Osteoporosis	$141	$139	$152
Paget's Disease	$2	$2	$3
Joints, Ligaments, and Connective Tissues*	$522	$520	$565
Temporomandibular Muscle/Joint Disorder	$15	$13	$14
Neurosciences	$6,460	$7,317	$8,224
Pain Research*	$483	$516	$605
Fibromyalgia	$11	$14	$14
Headaches	$24	$30	$32
Migraines	$18	$22	$21
Pain Conditions—Chronic	$410	$440	$474
Vulvodynia	$2	$1	$2
Reproductive System*	$1,115	$1,178	$1,236
Cervical Cancer	$99	$114	$112
Ovarian Cancer	$144	$151	$159
Prostate Cancer	$253	$239	$261
Uterine Cancer	$50	$45	$47
Vulvodynia	$2	$1	$2
Adolescent Sexual Activity	$91	$99	$96
Teenage Pregnancy	$14	$14	$17
Contraception/Reproduction	$419	$437	$496
Endometriosis	$10	$6	$7
Fibroid Tumors (Uterine)	$12	$11	$13
Infertility	$86	$94	$120

Appendix J:
EUREKA Prize Competitions

NIH uses prize competitions, also known as challenges, to spark new ways of thinking, solve tough problems, stimulate innovation, and advance its core mission of turning discovery into health. Prize competitions enable NIH ICs to establish ambitious goals without bearing high levels of risk by paying only for results. This mechanism also affords NIH the opportunity to engage innovators across the country who have a wide range of skill sets and diverse backgrounds, but who typically may not contribute to NIH research activities.

Section 2002 of the *21st Century Cures Act* (P.L. 114-255), enacted on December 13, 2016, requires NIH to support Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) prize competitions in areas of biomedical science that could: (1) realize significant advancements, and/or (2) improve health outcomes in human diseases and conditions that have a disproportionately small research investment relative to expenses for prevention and treatment, represent a serious and significant disease burden, or for which there is potential for significant return on investment. The *21st Century Cures Act* also requires NIH to report on the effect of innovations developed from EUREKA prize competitions on advancing biomedical science, improving health outcomes, and federal expenditures, and to include this information in the NIH triennial report. EUREKA prize competitions are carried out under authority granted to federal agencies by Section 24 of the *Stevenson-Wydler Technology Innovation Act of 1980* (15 U.S.C. 3719).

NIH, through NIA, began implementing the EUREKA prize authority in November 2017 through a request for public input on (1) the feasibility of three potential prize competitions focused on Alzheimer's disease (AD) and AD-related dementias (ADRD): validating predictors of AD progression; PET radiotracer to measure *in vivo* synaptic integrity; and low-cost innovation to improve systems of care for AD/ADRD patients and caregivers; and (2) any other suggestions for AD/ADRD research goals to connect to a prize.[1,2] These efforts culminated in NIA's launching the first EUREKA prize competition on September 10, 2019—The Improving Care for People with Alzheimer's Disease and Related Dementias Using Technology (iCare-AD/ADRD). The iCare-AD/ADRD Challenge offered cash prizes totaling $400,000 to spur and reward the development of solutions for a technology-based application, fostering connections between relevant stakeholders to use technology, or the development of new technology applications to improve dementia care coordination and navigation. Effective dementia care management has been shown to improve outcomes, for example, by reducing behavioral and psychological symptoms of dementia and lowering

[1] https://www.nih.gov/about-nih/who-we-are/nih-director/testimony-21st-century-cures-implementation-updates-fda-nih.
[2] https://grants.nih.gov/grants/guide/notice-files/NOT-AG-17-018.html.

health care costs by reducing emergency department visits, inpatient hospitalizations, and some readmissions.

Submissions for the iCare-AD/ADRD Challenge were accepted until June 30, 2019. Thirty-three innovative applications were submitted for consideration and NIA will announce up to three cash winners at the end of September 2019. The first-place winner will receive up to $250,000, the second-place winner will receive up to $100,000, and the third-place winner will receive up to $50,000. Additional solvers may be recognized with non-monetary awards.

Following this competition, NIA will monitor and measure the impact of the inaugural EUREKA prize competition and will report available information on its effects on research, health, and federal expenditures in the FY 2019–2021 report.

Appendix K:
Acronyms

Acronym	Meaning
2-D	two-dimensional
3-D	three-dimensional
3D-ROC	3-D Retina Organoid Challenge
7DHC	7-dehydrocholesterol
A2CPS	Acute to Chronic Pain Signatures
AA	Alzheimer's Association
AAAS	American Association for the Advancement of Science
AALD	alcohol-associated liver diseases
AAV	adeno-associated virus
ABCD	Adolescent Brain Cognitive Development
ACC	Autism Coordinating Committee
ACD	Advisory Committee to the Director
ACDC	arterial calcification due to deficiency of CD73
ACE	Autism Centers of Excellence
ACIP	Asthma Care Implementation Program
ACL	Administration for Community Living
ACOG	American College of Obstetricians and Gynecologists
ACP	advance care planning
ACT NOW	Advancing Clinical Trials in Neonatal Opioid Withdrawal
ACT NOW CE	Advancing Clinical Trials in Neonatal Opioid Withdrawal Current Experience
ACTC	Alzheimer's Clinical Trials Consortium
AD	Alzheimer's disease
AD/ADRD	Alzheimer's disease and Alzheimer's disease-related dementias
ADA	American Diabetes Association
ADAGES	African Descent and Glaucoma Evaluation Study
ADDM	Autism and Developmental Disabilities Monitoring
ADGC	Alzheimer's Disease Genetics Consortium
ADHD	attention deficit hyperactivity disorder
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADORE	Alzheimer's and Dementia Outreach, Recruitment, and Engagement Resources

Acronym	Meaning
ADRC	Alzheimer's Disease Research Center
ADRD	Alzheimer's disease-related dementias
ADSP	Alzheimer's Disease Sequencing Project
AEIO	Autism Evaluation Implementation Oversight
AFib	atrial fibrillation
AGI	Audacious Goals Initiative
AHEC	Area Health Education Center
AHRQ	Agency for Healthcare Research and Quality
AI/AN	American Indian/Alaska Native
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALF	acute liver failure
ALK	anaplastic lymphoma kinase
ALS	amyotrophic lateral sclerosis
AMA	American Medical Association
AMD	age-related macular degeneration
AMP	Accelerating Medicines Partnership
AMP-AD	Accelerating Medicines Partnership for Alzheimer's Disease
AMP-PD	Accelerating Medicines Partnership for Parkinson's Disease
AMR	antimicrobial resistance
ANS	autonomic nervous system
AnVIL	Analysis, Visualization, and Informatics Lab-space
AOSLO	adaptive optics scanning laser ophthalmoscope
aPAP	autoimmune pulmonary alveolar proteinosis
APFED	American Partnership for Eosinophilic Disorders
APIS	Alcohol Policy Information System
APOE	apolipoprotein E
APOLLO	Applied Proteogenomics OrganizationaL Learning and Outcomes
AR	androgen receptor
ART	antiretroviral therapy
AS	Angelman syndrome
ASCQ-Me	Adult SCD Quality of Life Measurement Information System
ASD	autism spectrum disorder
ASPREE	ASPirin in Reducing Events in the Elderly
ASRM	American Society for Reproductive Medicine
AT1	alveolar type 1
AT2	alveolar type 2
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
AUD	alcohol use disorder

Acronym	Meaning
BARDA	Biomedical Advanced Research and Development Authority
BD2K	Big Data to Knowledge
BDNF	brain-derived neurotrophic factor
BD-STEP	Big Data Scientist Training Enhancement Program
BEST	Broadening Experiences in Scientific Training
BETRNet	Barrett's Esophagus Translational Research Network
BG	blood glucose
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BMI	body mass index
bNAb	broadly neutralizing antibody
BP	blood pressure
BPA	bisphenol A
BPCA	*Best Pharmaceuticals for Children Act*
BP-ENDURE	NIH Blueprint-Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences
BPT	behavioral parent training
BRAIN	Brain Research through Advancing Innovative Neurotechnologies
BRAINS	Biobehavioral Research Awards for Innovative New Scientists
BRIDA	BACH2-related immunodeficiency and autoimmunity
BSSR	Behavioral and Social Sciences Research
Ca^{2+}	calcium
CAC	coronary artery calcium
CAR	chimeric antigen receptor
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CARDIA	Coronary Artery Risk Development in Young Adults
CARES	*Autism Collaboration, Accountability, Research, Education, and Support Act of 2014*
CBT	cognitive behavioral therapy
CC	NIH Clinical Center
CCDG	Centers for Common Disease Genomics
C-CHEM^2	Center for Children's Health, the Environment, the Microbiome, and Metabolomics
CCR	Center for Cooperative Resolution
CCTN	Contraceptive Clinical Trials Network
CDC	Centers for Disease Control and Prevention
CDE	Common Data Elements
CDK4/6	cyclin-dependent kinases 4 and 6
CEGIR	Consortium of Eosinophilic Gastrointestinal Disease Researchers

Acronym	Meaning
CEHN	Children's Environmental Health Network
CF	cystic fibrosis
CFAR	Centers for AIDS Research
CFS	chronic fatigue syndrome
CFTR	cystic fibrosis transmembrane conductance regulator
CHAPLE	complement hyperactivation, angiopathic thrombosis, protein losing enteropathy
CHIKV	Chikungunya virus
ChiLDReN	Childhood Liver Disease Research Network
CHW	community health worker
CIC	Cancer Immunotherapy Consortium
CIT	Center for Information Technology
CJD	Creutzfeldt-Jakob disease
CKD	chronic kidney disease
CKDu	chronic kidney disease of unknown origin
CL/P	cleft lip/palate
ClinGen	Clinical Genome Resource
CLOCK	circadian locomotor output cycles kaput
CMD	congenital muscular dystrophy
CMS	Centers for Medicare and Medicaid Services
COE	Center of Excellence
COG	Children's Oncology Group
CollegeAIM	College Alcohol Intervention Matrix
COMMAD	coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness
COPD	chronic obstructive pulmonary disease
COTC	Community Outreach and Translation Core
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CPAG	Coalition for Patient Advocacy Groups
CPCCRN	Collaborative Pediatric Critical Care Research Network
CPDPC	Chronic Pancreatitis Diabetes and Pancreatic Cancer
CPSTF	Community Preventive Services Task Force
CRC	Collaborative Research Center
CRDC	Cancer Research Data Common
CReATe	Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium
CREATE Bio	Cooperative Research to Enable and Advance Translational Enterprises for Biotechnology Products and Biologics

Acronym	Meaning
CREx	Collaborative Research Exchange
CRISPR/Cas9	clustered regularly interspaced short palindromic repeats associated protein 9
cryo-EM	cryo-electron microscopy
CSBC	Cancer Systems Biology Consortium
CSR	Center for Scientific Review
CSTN	Cardiothoracic Surgical Trials Network
CT	computed tomography
CTAC	Clinical Trials and Translational Research Advisory Committee
CTC	Communities That Care
CTE	chronic traumatic encephalopathy
CTN	Clinical Trials Network
CTP	Center for Tobacco Products
CTS	carpal tunnel syndrome
CTSA	Clinical and Translational Science Award
CTSI	Clinical Translational Science Institute
CURES	Center for Urban Responses to Environmental Stressors
CureSC	Cure Sickle Cell
CVD	cardiovascular disease
CWOW	Centers Without Walls
CYP	cytochrome P450
D&I	dissemination and implementation
DAA	direct-acting antiviral
DASH	Dietary Approaches to Stop Hypertension
DBA	Diamond-Blackfan anemia
dbGaP	Database of Genotypes and Phenotypes
DCCT	Diabetes Control and Complications Trial
DEAP	Data Exploration and Analysis Portal
DEBUT	Design by Biomedical Undergraduate Teams
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for the Ischemic Stroke
DENV	Dengue virus
DetectCID	Detecting Cognitive Impairment, Including Dementia
DFU	diabetic foot ulcer
DHFR	dihydrofolate reductase
DLK	dual leucine zipper kinase
DMCC	Data Management and Coordinating Center
DMD	Duchenne muscular dystrophy
DMF	dimethyl fumarate

Acronym	Meaning
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid
DoD	U.S. Department of Defense
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DR	diabetic retinopathy
DR2	Disaster Research Response
DRC	Democratic Republic of the Congo
DRCR.net	Diabetic Retinopathy Clinical Research Network
DSD	difference in sex development
DSLD	Dietary Supplement Label Database
EBOV	Ebola virus
EBV	Epstein-Barr virus
ECHO	Environmental Influences on Child Health Outcomes Program
e-cigarette	electronic cigarette
ED	emergency department
EDI	Office of Equity, Diversity, and Inclusion
EDIC	Epidemiology of Diabetes Interventions and Complications Study
EDRN	Early Detection Research Network
ED-SAFE	Emergency Department Safety Assessment and Follow-up Evaluation
ED-STARS	Emergency Department Screen for Teens at Risk for Suicide
EEG	electroencephalography
EHR	electronic health record
EHS	environment, health, and science
eMERGE	Electronic Medical Records and Genomics Network
ENDS	electronic nicotine delivery systems
ENDURE	Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences
EPA	U.S. Environmental Protection Agency
EPO	erythropoietin
EPPIC Net	Early Phase Preclinical Investigation Network
eRA	electronic Research Administration
eRNA	enhancer RNA
ESRD	end-stage renal disease
EVD	Ebola virus disease
exRNA	extracellular RNA
FAIR	findable, accessible, interoperable, and reusable

Acronym	Meaning
FASD	fetal alcohol spectrum disorder
FDA	U.S. Food and Drug Administration
FDAAA	*Food and Drug Administration Amendments Act of 2007*
FDAMA	*Food and Drug Administration Modernization Act of 1997*
FIC	John E. Fogarty International Center
FLS	fibroblast-like synoviocyte
FMD	flow-mediated dilation
fMRI	functional magnetic resonance imaging
FNIH	Foundation for the National Institutes of Health
FOA	funding opportunity announcement
FOP	fibrodysplasia ossificans progressiva
FSHD	facioscapulohumeral muscular dystrophy
FXTAS	fragile X-associated tremor/ataxia syndrome
FY	fiscal year
GAA	alpha-glucosidase
GAME-ON	Genetic Associations and Mechanisms in Oncology
GCAD	Genome Center for Alzheimer's Disease
GDC	Genomic Data Commons
GDM	gestational diabetes mellitus
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GLEE	Genomic Literacy, Education, and Engagement
GM	genetically modified
GPRA	*Government Performance and Results Act*
GRADE	Glycemia Reduction Approaches in Diabetes: An Effectiveness Study
GWAS	genome-wide association study
H3Africa	Human Health and Heredity in Africa
HA	hemagglutinin
HALT-MS	High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis
HAND	HIV-associated neurocognitive disorder
HANDLS	Healthy Aging in Neighborhoods of Diversity across the Life Span
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA	hemoglobin A
HBa1c	hemoglobin A1c
HbF	fetal hemoglobin
HBRN	Hepatitis B Research Network
HBV	hepatitis B virus
HCHS/SOL	Hispanic Community Health Study/Study of Latinos

Acronym	Meaning
HCMI	Human Cancer Model Initiative
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HDIT/HCT	high-dose immunosuppressive therapy and autologous hematopoietic cell transplant
HDV	hepatitis D virus
HEAL	The Helping to End Addiction Long-term℠ Initiative
HEPI	Health Professional Education Partnership Initiative
HER2	human epidermal growth factor receptor 2
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HHS	U.S. Department of Health and Human Services
HIRN	Human Islet Research Network
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMP	Human Microbiome Project
HNBP	Healthy Native Babies Project
HNSCC	head and neck squamous cell cancers
HO	heterotopic ossification
HPFH	hereditary persistence of fetal hemoglobin
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HRI	heme-regulated inhibitor
HRSA	Health Resources and Services Administration
HSV-1	herpes simplex virus-1
HTS	high-throughput screening
HuBMAP	Human BioMolecular Atlas Program
HZO	herpes zoster ophthalmicus
I statement	Insufficient Evidence statement
IACC	Interagency Autism Coordinating Committee
IADRP	International Alzheimer's and Related Dementias Research Portfolio
IASLC	International Association for the Study of Lung Cancer
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBSOS	IBS Outcome Study
IC/BPS	interstitial cystitis/bladder pain syndrome
ICAC	Inner-City Asthma Consortium
ICD	International Classification of Diseases

Acronym	Meaning
ICEMR	International Centers of Excellence for Malaria Research
ICOs	Institutes, Centers, and Offices
ICPC	International Cancer Proteogenome Consortium
ICs	Institutes and Centers
IDDRC	Intellectual and Developmental Disabilities Research Centers
IDeA	Institutional Development Award
IDeA-CTR	IDeA Program Infrastructure for Clinical and Translational Research
IDU	injection drug user
IeDEA	International Epidemiological Databases to Evaluate AIDS
Ig	immunoglobulin
IgE	immunoglobulin E
IHS	Indian Health Service
IMPAC	Information for Management Planning Analysis and Coordination
IMPRES	immuno-predictive score
INCLUDE	INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE
INSIGHT	Intervention Nurses Start Infants Growing on Healthy Trajectories
INSPPIRE	InterNational Study group of Pediatric Pancreatitis: In search for a cuRE
IOP	intraocular pressure
IPF	idiopathic pulmonary fibrosis
iPGM	cofactor-independent phosphoglycerate mutase
ipRGC	intrinsically photosensitive retinal ganglion cell
iPSC	induced pluripotent stem cell
IRACDA	Institutional Research and Academic Career Development Awards
IRB	institutional review board
IRP	Intramural Research Program
ISPCTN	IDeA States Pediatric Clinical Trials Network
ISS National Lab	International Space Station U.S. National Laboratory
IU	international unit
IV	intravenous
JCOIN	Justice Community Opioid Innovation Network
JIA	juvenile idiopathic arthritis
LABS	Longitudinal Assessment of Bariatric Surgery
LAD1	leukocyte adhesion deficiency type 1
LAM	lymphangioleiomyomatosis
LAP	localized aggressive periodontitis
LDN	Lysosomal Disease Network
LDRC	Learning Disabilities Research Centers

Acronym	Meaning
LEAP	Learning Early About Peanut Allergy
LGMD	limb-girdle muscular dystrophy
LI	lifestyle intervention
LIFE-Moms	Lifestyle Interventions for Overweight and Obese Pregnant Women
LMIC	low- and middle-income country
LookAHEAD	Action for Health in Diabetes
LRBA	lipopolysaccharide-responsive and beige-like anchor protein
LURN	Lower Urinary Tract Dysfunction Research Network
LUT	lower urinary tract
LUTS	lower urinary tract symptoms
LV	left ventricular
MACS	Multicenter AIDS Cohort Study
MAP-MISS	McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MARC	Maximizing Access to Research Careers
MATCH	Molecular Analysis for Therapy of Choice
MBSR	mindfulness-based stress reduction
MCCC	multiple complex chronic conditions
MD	muscular dystrophy
MD-CARE	Muscular Dystrophy Community Assistance, Research, and Education Amendments
MDCRC	Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers
MDHI	Myotonic Dystrophy Health Index
MDR	multidrug-resistant
MDR-TB	multidrug-resistant tuberculosis
ME	myalgic encephalomyelitis
MECP2	methyl CpG binding protein 2
MERIT-UC	Methotrexate Response in Treatment of Ulcerative Colitis
MESA	Multi-Ethnic Study of Atherosclerosis
MHE	multiple hereditary exostoses
mHealth	mobile health
MHRN	Mental Health Research Network
MI	myocardial infarction
MIRA	Maximizing Investigator Research Award
miRNA	microRNA
MITF	microphthalmia-associated transcription factor
MJFF	Michael J. Fox Foundation

Acronym	Meaning
MMP-7	matrix metalloproteinase-7
MoTrPAC	Molecular Transducers of Physical Activity Consortium
MRgFUS	magnetic resonance imaging-guided focused ultrasound surgery
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRS	magnetic resonance spectroscopy
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	multiple sclerosis
MSC	mesenchymal stem cell
MSM	men who have sex with men
MSTP	Medical Scientist Training Program
Mtb	*Mycobacterium tuberculosis*
MTF	Monitoring the Future
mTOR	mechanistic target of rapamycin
NA	neuraminidase
NACA	National Advisory Council on Aging
NACC	National Alzheimer's Coordinating Center
NAD	nicotinamide adenine dinucleotide
NAFLD	nonalcoholic fatty liver disease
NAO	National AHEC Organization
NAPA	*National Alzheimer's Project Act*
NARCH	Native American Research Centers for Health
NAS	neonatal abstinence syndrome
NASA	National Aeronautics and Space Administration
NASH	nonalcoholic steatohepatitis
NAVIGATE	NCI and VA Interagency Group to Accelerate Trials Enrollment
NCATS	National Center for Advancing Translational Sciences
NCBI	National Center for Biotechnology Information (at the NLM)
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NCIG	NIAAA Clinical Investigations Group
NCMRR	National Center for Medical Rehabilitation Research
NCORP	NCI Community Oncology Research Program
NCTN	National Clinical Trials Network
NCTRI	National Centers for Translational Research in Reproduction and Infertility
NDA	NIMH Data Archive
NDAR	National Database for Autism Research
NDEWS	National Drug Early Warning System

Acronym	Meaning
NEHEP	National Eye Health Education Program
NEI	National Eye Institute
NEIGHBOR	NEI Glaucoma Human genetics collaBORation consortium
NEO	NIH Ethics Office
NET	neutrophil extracellular trap
NF1	neurofibromatosis type 1
NFL	National Football League
NGRI	Next-Generation Researchers Initiative
NGS	next-generation sequencing
NHALES	Natural History of Asthma with Longitudinal Environmental Sampling study
NHGRI	National Human Genome Research Institute
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAGADS	NIA Genetics of Alzheimer's Disease Data Storage Site
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NLP	natural language processing
Nluc	Nano luciferase
NNLM	National Networks of Libraries of Medicine

Acronym	Meaning
NOAA	National Oceanic and Atmospheric Administration
NOSI	notice of special interest
NOWS	neonatal opioid withdrawal syndrome
NPC1	Niemann-Pick disease, type C1
N-PeRC	Trans-NIH Pediatric Research Consortium
NRFC	not recommended for further consideration
NRN	Neonatal Research Network
NRSA	National Research Service Award
NSAID	non-steroidal anti-inflammatory drug
NSF	National Science Foundation
NSIGHT	Newborn Sequencing in Genome Medicine and Public Health
NTP	National Toxicology Program
OA	osteoarthritis
OAIC	Older Americans Independence Center
OALM	Office of Acquisitions Logistics and Management
OAR	Office of AIDS Research
OBSSR	Office of Behavioral and Social Sciences Research
OCPL	Office of Communications and Public Liaison
OD	Office of the Director
ODP	Office of Disease Prevention
ODS	Office of Dietary Supplements
OER	Office of Extramural Research
OI	osteogenesis imperfecta
OIA	Outstanding Investigator Award
OIR	Office of Intramural Research
OIT	oral immunotherapy
OLPA	Office of Legislative Policy and Analysis
OM	Office of Management
ONSEN	Omics Nursing Science & Education Network
OPACH	Objective Physical Activity and Cardiovascular Health
OppNet	Opportunity Network
OPRC	Obstetric-Fetal Pharmacology Research Centers
ORDR	Office of Rare Diseases Research
OREC	Outreach, Recruitment, and Education Core
ORIP	Office of Research Infrastructure Programs
ORWH	Office of Research on Women’s Health
OSA	obstructive sleep apnea
OSP	Office of Science Policy
OTA	Other Transaction Authority

Acronym	Meaning
OTCD	ornithine transcarbamylase deficiency
OUD	opioid use disorder
OxCam	Oxford-Cambridge Scholars Program
P.L.	Public Law
P2P	Pathways to Prevention
PA	program announcement
PACE	Pregnancy and Childhood Epigenetics Consortium
PAG	patient advocacy group
PAP	pulmonary alveolar proteinosis
PCB	polychlorinated biphenyl
PCORI	Patient-Centered Outcomes Research Institute
PCOS	polycystic ovarian syndrome
PCRC	Palliative Care Research Cooperative
PD-1	programmed cell death protein 1
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFAS	per- and polyfluorinated alkyl substances
PHN	Pediatric Heart Network
PHR	patient health record
PHS	Public Health Service
PKCδ	protein kinase C delta
PLT	platelet
$PM_{2.5}$	particulate matter with aerodynamic size less than 2.5 μm
PMC	PubMed Central
PMI	Precision Medicine Initiative
PPI	proton pump inhibitor
PRCC	Prevention Research Coordinating Committee
PrecISE	Precision Interventions for Severe and Exacerbation Prone Asthma
PrEP	pre-exposure prophylaxis
PRGLAC	Task Force on Research Specific to Pregnant Women and Lactating Women
PRIDE	Program to Increase Diversity Among Individuals Engaged in Health-Related Research
PRISM	Pragmatic and Implementation Studies for the Management of Pain
PRISMS	Pediatric Research Using Integrated Sensor Monitoring Systems
PROSPR	Population-based Research to Optimize the Screening Process
PROTECT	Predicting Response to Standardized Pediatric Colitis Therapy
PS-ON	Physical Sciences-Oncology Network

Acronym	Meaning
PT/OT	physical therapy or occupational therapy
PTH	parathyroid hormone
PTSD	posttraumatic stress disorder
PUSH	Prevention of Urinary Stones with Hydration
PVD	provoked vestibulodynia
R&D	research and development
RA	rheumatoid arthritis
RBC	red blood cell
RCCN	Research Centers Collaborative Network
RCDC	Research, Condition, and Disease Categorization
RCMI	Research Centers in Minority Institutions
RCT	randomized controlled trial
RDA	*Rare Diseases Act of 2002*
RDCRC	Rare Diseases Clinical Research Consortia
RDCRN	Rare Diseases Clinical Research Network
RDCRN3	Rare Diseases Clinical Research Network, third cycle
RDCRN4	Rare Diseases Clinical Research Network, fourth cycle
REACT	Responsive Evaluation and Assessment of Chemical Toxicity
REDS	Recipient Epidemiology and Donor Evaluation Study
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RePORT	NIH Research Portfolio Online Reporting Tools
RESPOND	Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress
RFA	request for applications
RFI	request for information
RGC	retinal ganglion cell
RIC	Recruitment Innovation Center
RISE	Restoring Insulin Secretion
RNA	ribonucleic acid
ROCS	Research on Cancer Survivors
RPE	retinal pigment epithelium
RPG	research project grants
RRMS	relapsing-remitting multiple sclerosis
RSV	respiratory syncytial virus
rTMS	repetitive transcranial magnetic stimulation
RVO	retinal vein occlusion
RyLAN	red cell and leukocyte antigen
S2P	site-2-protease
S2S	Screen to Save

Acronym	Meaning
SABV	sex as a biological variable
SAMHSA	Substance Abuse and Mental Health Services Administration
SARP	Severe Asthma Research Program
SBIR	Small Business Innovation Research
SCD	sickle cell disease
SCDIC	SCD Implementation Consortium
SCLC	small cell lung cancer
SCOR	Specialized Center of Research
SCORE	Support of Competitive Research
SEARCH	Search for Diabetes in Youth
SEER	Surveillance, Epidemiology, and End Results
SEPA	Science Education Partnership Award
SES	socioeconomic status
SGFS	Secondary Genomics Finding Service
SGM	sexual and gender minority
SGMRO	Sexual & Gender Minority Research Office
SHINE	Stimulating Hematology Investigation New Endeavors
SIG	Scientific Interest Group
SIK2	salt-inducible kinase 2
SIREN	Strategies to Innovate Emergency Care Clinical Trials Network
siRNA	silencing RNA
SIV	simian immunodeficiency virus
sJIA	systemic juvenile idiopathic arthritis
SLE	systemic lupus erythematosus
SLOS	Smith-Lemli-Opitz syndrome
SMART	Streamlined, Multisite, Accelerated Resources for Trials
SNP	single-nucleotide polymorphism
SPAN	Stroke Preclinical Assessment Network
SPIRIT	Suicide Prevention for at-Risk Individuals in Transition
SPIROMICS	Subpopulations and Intermediate Outcome Measures in COPD
SPORE	Specialized Programs of Research Excellence
SPORT	Spine Patient Outcomes Research Trial
SPRINT	Systolic Blood Pressure Intervention Trial
SPRINT-MS	Safety, Tolerability and Activity Study of Ibudilast in Subjects with Progressive Multiple Sclerosis
SREI	Society for Reproductive Endocrinology and Infertility
SRG	Scientific Review Group
SSc	systemic sclerosis
STAR	Supplements to Advance Research

Acronym	Meaning
StARR	Stimulating Access to Research in Residency
STaRS	Science, Teachers, and Research Summer
STEM	science, technology, engineering, and mathematics
STR	State Targeted Response
STRIDE	Strategies to Reduce Injuries and Develop Confidence in Elders
STRIDE-2	Hematopoietic Stem Cell Transplantation for Young Adults with Sickle Cell Disease
STRIDES	Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability
STTR	Small Business Technology Transfer
SUD	substance use disorder
SUID	sudden unexpected infant death
SWAN	Study of Women's Health Across the Nation
TAC	Tribal Advisory Committee
TARGET	Therapeutically Applicable Research to Generate Effective Treatments
TAVR	transcatheter aortic valve replacement
TB	tuberculosis
TBD	tickborne disease
TBI	traumatic brain injury
TB-PET	total-body positron emission tomography
TCC	Transdisciplinary Collaborative Centers
TCD	transcranial Doppler
TCFA	thin-cap fibroatheroma
TCGA	The Cancer Genome Atlas
TCTC	Tissue Chip Testing Centers
TCU	Tribal College and University
TEC	Tribal Epidemiology Centers
TEDDY	The Environmental Determinants of Diabetes in the Young
TGFβ	transforming growth factor beta
TGNC	transgender or gender nonconforming
Th17	T helper cells
THR	therapeutic horseback riding
THRO	Tribal Health Research Office
TIN	Trial Innovation Network
TMIST	Tomosynthesis Mammography Imaging Screening Trial
TOPMed	Trans-Omics for Precision Medicine
Tox21	Toxicology in the 21st Century Program
TRK	tropomyosin receptor kinase

Acronym	Meaning
TRND	Therapeutics for Rare and Neglected Diseases
TRSP	Tobacco Regulatory Science Program
TSC	tuberous sclerosis complex
TWiTCH	Transcranial Doppler with Transfusions Changing to Hydroxyurea
U.S.C.	United States Code
UAE	uterine artery embolization
UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco
UDN	Undiagnosed Diseases Network
UI	urinary incontinence
UPEC	uropathogenic *Escherichia coli*
USDA	U.S. Department of Agriculture
USDRN	Urinary Stone Disease Research Network
USPSTF	U.S. Preventive Services Task Force
U-STAR	Undergraduate Student Training in Academic Research
UT	The University of Texas
UTI	urinary tract infection
VA	U.S. Department of Veterans Affairs
VCID	Vascular Contributions to Cognitive Impairment and Dementia
VDAART	Vitamin D Antenatal Asthma Reduction Trial
VDORA1	Vitamin D Supplementation in Children with Obesity-Related Asthma
VHA	Veterans Health Administration
VLP	virus-like particle
VOC	vaso-occlusive crisis
VR	virtual reality
VSV	vesicular stomatitis virus
VTE	venous thromboembolism
VZV	Varicella-zoster virus
WE-HEAL	Wound Etiology and HEALing
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WNV	West Nile virus
WRAIR	Walter Reed Army Institute of Research
XLH	X-linked hypophosphatemia
Ybt	yersiniabactin
Yp	*Yersinia pseudotuberculosis*
ZIKV	Zika virus
ZIP	Zika in Infants and Pregnancy

Acronym	Meaning
ZIRC	Zebrafish International Resource Center