Report of the Director
National Institutes of Health

Fiscal Years 2014 & 2015

National Institutes of Health
Turning Discovery Into Health

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Preface

This is the fifth National Institutes of Health (NIH) Biennial Report that is required by Section 403 of the *Public Health Service (PHS) Act*. (See Appendix A of this report for language in the *PHS Act* that is relevant to this report.) 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. It then describes NIH structure, policies, and procedures. Chapter 1 focuses on operations of NIH extramural and intramural research programs, and mechanisms for strategic planning. This chapter also addresses various cross-cutting activities that are not covered elsewhere in the report, such as programs that provide the platform for discovery, including science literacy efforts and training and career development activities.

Chapter 2 provides an overview of the NIH research portfolio. Topics include:

- Basic Research
- Preclinical Translational Research
- Clinical Research
- Postclinical Translational Research
- Clinical and Community Practice
- Epidemiology — Identifying Public Health Needs
- Infrastructure, Research Resources, and Technology Development

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[1] 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 year (FY) 2014 and 2015 reporting period. Topics include:

- 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

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

Each of these topics, many of which are categories specified in the *PHS Act*, are 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 2014 and 2015 (covering programmatic and research activities and 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 the *Common Fund Strategic Planning Report of 2015*.
- Appendix D lists the NIH ICs and OD offices, and provides links to the missions and strategic plans, where relevant.
- Appendix E consists of 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 includes NIH funding levels for chronic diseases and organ systems.
- Appendix J contains a list of acronyms that are used in this *Biennial Report*.

Contents

Chapter 1 About NIH

Statement of the Director

It is my honor to present to Congress the Biennial Report of the Director of the National Institutes of Health (NIH) for Fiscal Years (FY) 2014 and 2015. With Congressional support, NIH continues the discovery of fundamental knowledge about the nature and behavior of living systems and how application of that knowledge can extend healthy life and reduce illness 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 across the globe.

Remarkable Contributions

For more than 125 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. Begun as a one-room Laboratory of Hygiene in 1887, NIH has grown into a complex and multidisciplinary engine for discovery and innovation comprised of 27 Institutes and Centers (ICs).

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. U.S. life expectancy has increased dramatically over the past century; between 1970 and 2010, the life expectancy of the average American increased by 7.9 years.[2] A baby born in 2014 can look forward to an average life span of more than 78 years, almost three decades longer than a baby born in 1900.[3] The infant mortality rate in the U.S. has decreased from 26 of every 1,000 births in 1960[4] to 5.8 per 1,000 births in 2014,[5] and the outlook for premature infants also has improved substantially.

[2] Calculated from Health, United States, 2011: with Special Feature on Socioeconomic Status and Health, http://www.cdc.gov/nchs/data/hus/hus11.pdf.
[3] National Vital Statistics Reports, Volume 65, Number 4, June 30, 2016. Deaths: Final Data for 2014. Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf.
[4] MacDorman ME, Rosenberg HM. *Vital Health Stat* 1993;20(20).
[5] National Vital Statistics Reports, Volume 65, Number 4, June 30, 2016. Deaths: Final Data for 2014. Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf.

In recent years, we have made impressive gains 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.[6] Between 1968 and 2013, deaths due to both coronary heart disease and stroke decreased by approximately 78 percent.[7] 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.[8] Moreover, the percentage of all deaths attributed to heart disease and cancer, which accounted for 60 percent of all deaths at their peak in 1983, dropped to 46 percent of deaths in 2013.[7]

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. Overall cancer death rates have dropped by about 1.5 percent per year, or nearly 15 percent in total from 2003 to 2012. The American Cancer Society estimates that 1.7 million cancer deaths (nearly 1.2 million men and half a million women) were averted from 1991 to 2012 by improvements in cancer treatment, detection, and prevention.[9] NIH-funded research has helped to identify major cancer subtypes and 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.[10]

One of NIH's greatest achievements over the past 30 years has been to lead the global research effort against the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) pandemic. Starting with basic research about how HIV works, discoveries along the biomedical 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. An HIV diagnosis was once a death sentence; now, an HIV-positive 20-year-old living in the U.S. who receives these treatments is expected to live into his or her early 70s, nearly as long as someone without HIV.[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 HIV-positive mothers. 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

[6] Fox CS, et al. *Circulation* 2004;110(5)522–7. PMID: 15262842.
[7] https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf.
[8] https://www.niddk.nih.gov/about-niddk/research-areas/diabetes/diabetes-prevention-program-dpp/Pages/default.aspx
[9] Siegel RL, et al. *CA Cancer J Clin* 2016;66(1):7-30. PMID: 26742998.
[10] http://www.cancer.gov/research/areas/treatment/immunotherapy-using-immune-system.
[11] Samji H, et al. *PLoS One* 2013;8(12). PMID: 24367482.

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 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, and the first large clinical trials of lithium as a mood stabilizer, supporting its U.S. Food and Drug Administration (FDA) approval in 1970. NIH-funded research established the first FDA-approved treatment for the most common type of stroke, a drug called tissue plasminogen activator, in 1995.[13] NIH scientists also pioneered therapies for rare diseases, including developing and testing the first cell-targeted enzyme replacement therapy for Gaucher disease,[14] and the first treatment of the rare disease lipodystrophy using a synthetic form of the fat-derived hormone leptin,[15] both of which went on to become FDA-approved therapies (in 1991 and 2014, respectively). NIH-funded research also helped lead to the development of tofacitinib (approved by the FDA in 2012), the first new rheumatoid arthritis drug in more than a decade that can be taken as a pill (rather than an injection) to slow or halt joint damage.

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 99 percent. NIH 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.

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 for the last 60 years by supporting a robust academic community that generates biomedical knowledge, patentable inventions, and trained scientists, including more than 140 NIH-funded Nobel laureates as of 2015. NIH funding supports research personnel at more than 2,500 institutions that are located in all 50 states, U.S. territories, and more than 90 countries around the world.

Investing in NIH propels the U.S. economy through job creation and support of scientific enterprises such as small biotechnology companies and scientific equipment sales. For example, a Battelle 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.[16] On a broader

[12] http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Prevention/Pages/perinatal.aspx.
[13] http://www.cdc.gov/stroke/types_of_stroke.htm.
[14] https://irp.nih.gov/accomplishments/therapy-for-inherited-enzyme-deficiencies.
[15] https://irp.nih.gov/accomplishments/from-hormone-to-pharmaceutical-lipodystrophy.
[16]. http://web.ornl.gov/sci/techresources/Human_Genome/publicat/2013BattelleReportImpact-of-Genomics-on-the-US-Economy.pdf.

scale, a United for Medical Research report shows that in 2015, NIH supported 352,000 jobs across all 50 states, including almost every congressional district.[17] Every dollar invested by NIH gives back to our nation in multiple; for example, NIH extramural funding generated some $60.7 billion new economic activity nationwide in 2015—nearly double taxpayers' investment.[17]

NIH-supported research also provides a foundation of scientific evidence that 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.[18,19] 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 eight years, and a $1.00 increase in public *clinical* research stimulates an additional $2.35 of industry R&D investment after three years.[19] NIH also partners with the private sector to drive discovery forward. In 2014, the Accelerating Medicines Partnership (AMP) among NIH, the U.S. Food and Drug Administration (FDA), 10 biopharmaceutical companies, and multiple non-profit organizations was launched. AMP seeks to increase the number of new diagnostics and therapies for patients while also reducing the time and cost of their development. Close to $230 million will be invested over five years, with total costs shared equally among NIH and the industry partners.[20]

NIH-funded research also helps to develop treatments, cures, and prevention strategies that reduce the economic burden of health care costs by replacing or averting expensive medical conditions and procedures. For example, the knowledge gained from an NIH-funded clinical trial on postmenopausal hormone therapy was found to have long-term financial and health outcomes worth an estimated $37.1 billion in net economic gain since the study was published in 2002, a return of approximately $140 on every dollar invested in the trial.[21] Cochlear implants, a technology developed in part with NIH support and which allows children with severe hearing loss to regain the ability to perceive and understand speech, have been found to save society more than $30,000 per child in medical and special education costs.[22] NIH-supported research also has developed evidence-based, early childhood interventions that have positive long-term effects on substance use and related behavioral health problems in adolescence and beyond, with savings ranging from $2.88 to as much as $25.92 per dollar invested.[23] As NIH-supported interventions lead to healthier lives, reduced medical costs and more productive citizens lead to a healthier economy.

NIH funding is the foundation for long-term U.S. global competitiveness in industries such 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

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[17] http://www.unitedformedicalresearch.com/wp-content/uploads/2016/05/NIH-Role-in-the-Economy-FY15-FINAL-5.23.16.pdf.
[18] http://www.nber.org/papers/w20889.
[19] Toole AA. *J Law Econ* 2007;50:81-104. http://sciencepolicy.colorado.edu/students/envs_5100/Toole2007.pdf.
[20] https://www.nih.gov/news-events/news-releases/nih-industry-non-profits-join-forces-speed-validation-disease-targets.
[21] Roth JA, et al. *Ann Intern Med* 2014;60(9):594-602. PMID: 24798522.
[22] Semenov YR, et al. *Ear Hear* 2013;34(4):402-12. PMID: 23558665.
[23] https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/early_childhood_prevention_march_2016.pdf.

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.

Advancing Science Through New Technologies

Since its launch in 2013, the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative has aimed to create a revolutionary picture of the brain that shows dynamic interactions between individual cells and complex neural circuits. Spurring development and application of innovative technologies to facilitate this work will fill current knowledge gaps in how the brain works and provide extraordinary opportunities to explore the intricacies of how the brain functions in real time. In turn, this could lead to new ways to treat, cure, or even prevent brain disorders. To outline the path forward that could lead to such breakthroughs, NIH convened a working group of the Advisory Committee to the NIH Director. This group developed BRAIN 2025: A Scientific Vision (June 2014),[24] which outlined a 12-year timeframe for the project and identified seven research goals along with milestones and deliverables. In September 2014, NIH announced its first wave of BRAIN-related grant awards, focusing on new tools and techniques to capture and understand brain function. In FY 2015, NIH nearly doubled that investment to ramp up activities in the second year. Together with other federal and industry partners, NIH will continue to work toward the goal of understanding how the brain works at the speed of thought (see the Neuroscience section of Chapter 3 for more updates on the BRAIN Initiative).

New gene-editing technology also is showing potential for transformational change in therapeutic options for genetic diseases. This technology, called CRISPR (clustered regularly interspaced short palindromic repeats), was named *Science* magazine's Breakthrough of the Year for 2015. The technique enables scientists to perform microsurgery on the genome, targeting genes for deletion, addition, activation, or suppression with incredible specificity. Using this system, researchers have altered DNA in human cells, rats, mice, zebrafish, bacteria, fruit flies, yeast, nematodes, and crops. Compared to other genome editing methods, CRISPR is comparatively easy and inexpensive; NIH is supporting many scientists who are investigating the possibilities of this approach, from generating viral resistance to investigating what genes might be involved in resisting cancer treatment. NIH-supported researchers will continue to push the boundaries of this method, along with careful consideration of the ethical, safety, and security questions that accompany genetic engineering.

NIH is investing in innovative technology to improve the drug development pipeline that would get more effective treatments to patients more quickly. Moving promising therapeutic compounds from basic research to clinical use is often met with significant bottlenecks, and drug toxicity is a common reason for failure. In 2012, NIH initiated the Tissue Chip for Drug Screening program, led by National Center for Advancing Translational Sciences (NCATS) and supported by the Common Fund. This program aims to develop human microsystems, or *organs-on-a-chip*, to enable earlier safety and toxicity testing for potential therapeutic compounds. These microsystems use cell types that reflect the biology of different

[24] https://www.braininitiative.nih.gov/2025/index.htm.

organs and tissues. FY 2014 awards for this program moved beyond the first phase of single organ-on-a-chip development and focused on integrating organs together and validating their function. Scientists are already demonstrating positive outcomes on a liver-gut-kidney-blood-brain barrier integration project and a heart-liver vasculature project. This integration will allow researchers to determine how drugs metabolized by one organ affect other organs or systems. Researchers also have produced neural tissue chips that have many features in common with the developing brain, and have created a placenta-on-a-chip to conduct experiments on that poorly understood organ.

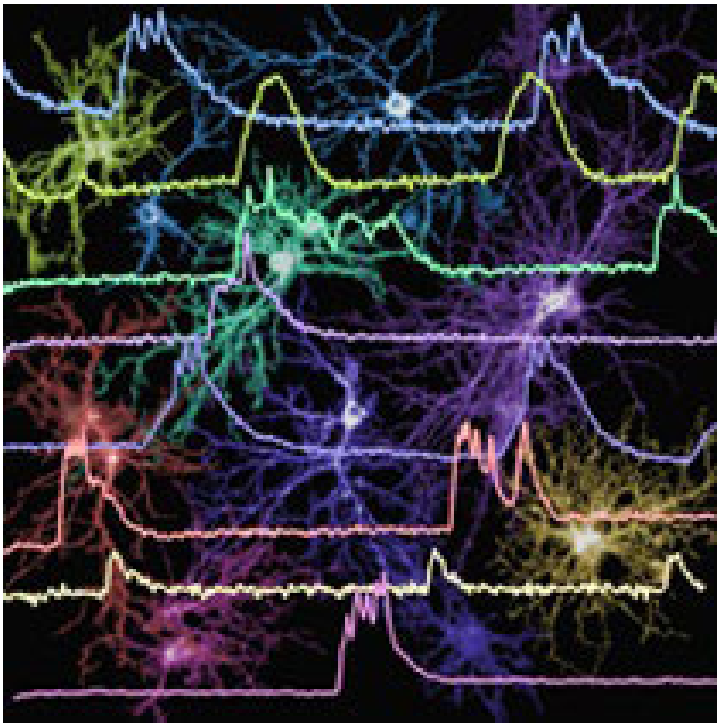

Figure 1. Scientists funded by the NIH BRAIN Initiative will develop tools to simultaneously watch the unique firing patterns of many neurons in hopes of classifying them based on physical characteristics, such as size and shape, and functional characteristics, such as patterns of electrical activity. Credit: Vincent Pieribone, Ph.D., John B. Pierce Laboratory, Inc.

The Age of Big Data

In response to the incredible growth in the volume, speed of delivery, and complexity of large biomedical datasets, NIH launched the Big Data to Knowledge (BD2K) initiative in 2012. Supported by the Common Fund, BD2K aims to facilitate broad use of biomedical big data; to develop new methods, software, and tools to analyze it; to enhance training in its development and use; and to support a data ecosystem that integrates big data and data science into biomedical research to accelerate discovery. Toward this goal, NIH announced the first round of grant awards in FY 2014, investing nearly $32 million in centers of excellence, a data discovery consortium, and training. In FY 2015, NIH made additional awards to expand the centers of excellence, support software development, and facilitate access to cloud computing resources, as well as to increase support for training through career development awards, institutional training grants for graduate students, and grants to develop training courses and open-education resources. In an ambitious pilot project, NIH also is planning to develop a Data

Commons as a way to store, share, access, and interact with data generated from biomedical research. The Data Commons will be cloud based so that researchers can access the data easily, enabling them to extract additional insights. NIH's investments in big data infrastructure and training will help prepare the biomedical research enterprise for the onslaught of data generated by technological advances.

One project that generated an immense amount of data came to a conclusion in 2015, exceeding expectations and creating a valuable resource for studies related to genomic variation in health and disease. The 1000 Genomes Project[25] sequenced the genomes of more than 2,500 people from 26 populations around the world. This effort from an international team of scientists identified and catalogued more than 99 percent of common human genomic variants (specifically, those *DNA spelling differences* with a frequency of at least 1 percent) as well as many rare variants.[26] This information can be used to study the frequency of a genomic variant and its potential disease relevance, as well as the demographics and history of the human population. These data also can be combined with genome-wide association studies (GWAS), which compare the genomes of people with and without a disease to find genomic variants associated with that disease to help identify the regions linked to a disease more precisely.

Genomic research advances our understanding of factors that influence health and disease, and sharing genomic data provides opportunities to accelerate that research through the power of combining large and information-rich datasets. To promote robust sharing of human and non-human data from a wide range of genomic research and to provide appropriate protections for research involving human data, NIH issued the *NIH Genomic Data Sharing (GDS) Policy* on August 27, 2014.[27] Among the expectations for studies that fall under the *GDS Policy* are the submission of a genomic data sharing plan prior to award, registration of all studies with human genomic data in the NIH database of Genotypes and Phenotypes (dbGaP), and the need for informed consent from patients for their genomic data to be used for future research and broad sharing. NIH has longstanding policies to make a wide range of data, including genomic data, from the research that it funds publicly available in a timely manner.

In other efforts to ensure that NIH-funded research is widely shared and publicly accessible, NIH issued its *Plan for Increasing Access to Scientific Publications and Digital Scientific Data from NIH Funded Scientific Research*[28] in February 2015. This plan was created in response to an Executive Order[29] that aimed to ensure that peer-reviewed publications and scientific data resulting from federally funded scientific research was accessible to the public and other scientists to the greatest possible extent. NIH's plan reinforces its 2008 *NIH Public Access Policy*,[30] requiring scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive *PubMed Central* no later than 12 months after publication. The plan also addresses digital scientific data, including requiring investigators to develop data management plans, encouraging the use of established public repositories and

[25] http://www.internationalgenome.org/.
[26] 1000 Genomes Project Consortium, et al. *Nature* 2015; 526(7571):68-74. PMID: 26432245.
[27] https://www.nih.gov/news-events/news-releases/nih-issues-finalized-policy-genomic-data-sharing.
[28] https://grants.nih.gov/grants/NIH-Public-Access-Plan.pdf.
[29] https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/ostp_public_access_memo_2013.pdf
[30] https://publicaccess.nih.gov/policy.htm.

community-based standards, and promoting data interoperability and openness. NIH also will explore the possibility of requiring NIH-funded investigators to make the data underlying their conclusions freely available in public repositories. Collectively, these policies to increase sharing and access to scientific data will support NIH's mission of expanding the biomedical research knowledge base as well as ensure a high return on the public's investment.

Rising to Public Health Challenges

In 2014, an outbreak of Ebola virus disease (EVD) in West Africa (Guinea, Liberia, and Sierra Leone) brought the world together to fight the epidemic and prevent its spread. This outbreak is the most severe EVD outbreak on record, generating more cases and deaths (more than 11,000) than the prior 24 EVD outbreaks combined. Having already conducted some research on this type of virus, NIH is leading development of therapeutics and vaccines, as well as faster diagnostic tools that can be used in the field. ZMapp, a monoclonal antibody treatment for EVD, is showing promising results for clearing the disease. The drug's development was supported by the National Institute of Allergy and Infectious Diseases (NIAID) and Mapp Pharmaceutical; it is being tested against the normal standard of care for EVD in a randomized clinical trial in West Africa. NIAID also is conducting and supporting the development of multiple vaccine candidates against EVD, including an intranasal vaccine that recently entered a Phase 1 clinical trial to test its safety in humans. In addition, NIH successfully treated two patients with EVD in the Clinical Center's Special Clinical Studies Unit, which is specifically designed to provide high-level isolation capabilities, and is staffed by infectious diseases and critical care specialists. The agency's response to this EVD outbreak illustrates how NIH cultivates its research and resources to facilitate swift action to combat and mitigate public health crises.

Figure 2. NIH Director Dr. Francis Collins, NIAID Director Dr. Anthony Fauci, and NIH Clinical Center Director Dr. John Gallin exit the Clinical Center in October 2014 with recently discharged Ebola patient Ms. Nina Pham. Credit: Bill Branson, NIH.

Fostering a Diverse Workforce

Innovation and scientific problem solving require diverse perspectives. NIH appointed a Chief Officer for Scientific Workforce Diversity in 2014 to lead NIH's efforts to recruit and retain the best and brightest science researchers. Simultaneously, to ensure a vibrant, dynamic research community, NIH embarked on a new program in FY 2014 to enhance the diversity of the biomedical research workforce. The Diversity Program Consortium (DPC),[31] supported by the Common Fund and managed by the National Institute of General Medical Sciences (NIGMS), aims to develop, implement, assess, and disseminate innovative and effective approaches to research training and mentoring. The DPC boasts of three integrated initiatives: Building Infrastructure Leading to Diversity (BUILD), the National Research Mentoring Network (NRMN), and a Coordination and Evaluation Center (CEC) to coordinate and evaluate outcomes of all DPC activities. The BUILD awards, made to undergraduate institutions, will help determine the most effective ways to engage and retain students from diverse backgrounds in biomedical research. The NMRN is developing a national network of mentors and mentees to provide guidance and resources for individuals from undergraduate to early career faculty levels. Together, these and other initiatives will help prepare students with varied backgrounds for careers in biomedical research.

Embracing New Scientific Opportunities

One of NIH's most ambitious new projects is the Precision Medicine Initiative (PMI), launched in January 2015. Precision medicine is an approach to prevention and treatment of disease that takes individual variation (e.g., genetics, environmental factors) into account. This approach already has success stories, including improved cancer treatment and rapid and accurate diagnosis of infectious agents. PMI will focus on two areas: (1) cancer clinical trials that use a patient's genetics to match them with a treatment option that is most likely to work for them; and (2) building a large U.S. research cohort to gather data on individuals that will help researchers develop precision medicine approaches to help patients.[32] This cohort will include one million or more participants of all ages, health statuses, and races/ethnicities, with a focus on including underserved populations. This cohort of more than a million people will enable researchers to study numerous diseases to find trends, commonalities, and differences that might lead to new and more effective interventions. Representing a new era of treatment and prevention of disease, this groundbreaking NIH effort will accelerate research and improve health.

—Francis S. Collins, M.D., Ph.D.

[31] https://www.nigms.nih.gov/training/dpc/Pages/default.aspx; also known as the Enhancing the Diversity of the NIH-Funded Workforce program.

[32] The PMI Cohort Program was renamed the *All of Us* Research Program in October 2016. 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.

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
- The processes of human growth and development
- The biological effects of environmental contaminants
- The understanding of mental, addictive, and physical disorders
- Directing 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

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 $30 billion budget.[33] The leadership and financial support NIH provides to biomedical, behavioral, and social science researchers extends throughout our nation and the world.

Figure 3. 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., 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 ICs *support* research and research training through extramural activities; most ICs also *conduct* research and research training through intramural activities.

Listing of ICs

The following is a list of NIH ICs. The ICs are presented in the order in which they appear on the appropriation table in the Congressional Justification. Appendix D provides web links to the mission statements and strategic plans of each IC. These mission statements and strategic plans classify and justify NIH priorities. 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 the Office of Intramural Research (OIR) that preserves records of significant NIH achievements,

[33] http://www.nih.gov/about/almanac/appropriations/part2.htm.

innovative exhibits, and educational programs to enhance understanding of NIH biomedical and behavioral research.

Institutes and Centers:

- 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 of select OD offices that advise the NIH Director, develop NIH policy, and provide essential NIH-wide oversight and coordination. The Offices are presented in the order in which they appear on the appropriation table in the Congressional Justification. Appendix D provides web links to the mission statements and strategic plans of OD program offices. These mission statements and strategic plans classify and justify NIH priorities.

Office of the Director:

- 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 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 Common Fund; the Office of AIDS Research (OAR); the Office of Behavioral and Social Sciences Research (OBSSR); the Office of Research Infrastructure Programs (ORIP); and the Office of Research on Women's Health (ORWH).[34] 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.

The Common Fund was enacted into law by Congress through the 2006 *NIH Reform Act* to support cross-cutting, 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

[34] Appendix B includes the web address of the *Report of the Advisory Committee on Research on Women's Health* for FY 2013 and 2014, which provides a summary of ORWH's accomplishments during this period.

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*.

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 (5-10 years).
- *Synergistic.* Outcomes must synergistically promote and advance individual missions of NIH Institutes and Centers to benefit health.
- *Cross-cutting.* Program areas must cut across missions of multiple NIH Institutes and Centers, 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.

Appendix C includes the address of the website where the *Common Fund Strategic Planning Report* may be found.

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 as well as 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 the 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 Office of Dietary Supplements, also included as an administrative unit within ODP, stimulates and supports scientific research in the area of dietary supplements.

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).

Office of Extramural Research

OER 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 Laboratory Animal Welfare; the Office of Policy for Extramural Research Administration; the Office of Extramural Programs; the Office of Research Information Systems; the Office of Planning, Analysis, and Communication; the Office of Data Analysis Tools and Systems; and the Office of Administrative Operations.

Office of Intramural Research

OIR 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; and the Office of Animal Care and Use.

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 $8 of every $10 appropriated to NIH 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 approximately 2,500 organizations, including universities, medical schools, hospitals, 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 2015, NIH funded the research of approximately 35,000 principal investigators through research grants, and the projects 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 coordination, compliance, and services converge to support and sustain the NIH extramural research program.

A key service OER provides for the NIH grants program is the electronic Research Administration (eRA) system. 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, and supports more than 160,000 extramural investigators worldwide.

Grants Overview

NIH announces the availability of funds for grant programs by issuing Funding Opportunity Announcements (FOAs)[35] in the *NIH Guide for Grants and Contracts*[36] and on the *Grants.gov* website. 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), as well as other types of FOAs in targeted areas of research identified through strategic planning. Because many FOAs are trans-NIH opportunities, their preparation can involve considerable collaboration.

The main types of grant funding that NIH provides are Research Grants (R series), Career Development Awards (K series), Research Training and Fellowships (T and F series), and Program Project/Center Grants (P series). NIH uses activity codes that incorporate the funding series to differentiate the wide variety of research and research-related awards NIH makes. The most commonly used activity code is the R01, which designates a grant for a discrete, specified research project that is generally awarded for three to five years. Receiving a first R01 is a significant professional achievement for a scientist, traditionally marking attainment of scientific independence. Examples of other activity codes are:

- R41/R42 and R43/R44 for the Small Business Technology Transfer program and the Small Business Innovation Research program, respectively
- R21 for exploratory/developmental research projects
- R15 for Academic Research Enhancement Awards that support small-scale research projects at educational institutions that have not been major recipients of NIH research grants
- R24 for research projects that will enhance the capability of resources to serve biomedical research
- R25 for research education projects
- F32 for postdoctoral individual fellowships under the National Research Service Award (NRSA)
- T32 for enabling institutions to make several NRSAs for both predoctoral and postdoctoral training
- K08, a career development award, for providing support and “protected time” to individuals with a clinical doctoral degree for an intensive, supervised research career development experience

[35] 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, solicitations, or parent announcements.
[36] http://grants.nih.gov/grants/guide.

- P01 for research program projects that are broadly based, multidisciplinary, often long-term research, and have a specific major objective or a basic theme
- P30 for shared resources and facilities at research centers

ICs vary in the extent to which they use various activity codes.

Some funding mechanisms are applied to unique grant activities. For example, NIEHS supports P42 grants, which are part of the Superfund Research Program, a network of university grants designed to seek solutions to the complex health and environmental issues associated with the nation's worst hazardous waste sites. The program's research is funded and administered by NIEHS in coordination with the U.S. Environmental Protection Agency (EPA), which is the federal entity charged with cleaning up these sites, and the HHS Agency for Toxic Substances and Disease Registry (ATSDR).

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. Research contracts are awarded to universities, nonprofit organizations, and for-profit organizations. NIH announces contract opportunities in the *NIH Guide for Grants and Contracts*[37] and on the federal wide *FedBizOpps.gov* website.[38]

Alternative Funding Mechanisms

In addition to the grants and contracts processes, some ICs may utilize alternative funding mechanisms such as challenges and Other Transaction Authority (OTA) to stimulate research. Challenge competitions appeal to a diverse audience who help to drive innovation and solve mission-centric problems, often through crowdsourcing.[39] OTA is a funding mechanism that targets non-traditional sources and allows a high degree of flexibility in how an agreement is awarded. Typical government procurement and grant laws, regulations, and policies do not apply to OTA awards.[40]

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[37] http://grants.nih.gov/grants/guide/description.htm.
[38] http://www.FedBizOpps.gov.
[39] https://www.challenge.gov/about/.
[40] https://www.nih.gov/precision-medicine-initiative-cohort-program/frequently-asked-questions-other-transaction-awards.

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 and make recommendations concerning programmatic relevance and funding. 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.[41]

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 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.

As noted above, the first level of review is conducted by SRGs that evaluate and give expert advice 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 budget and period of support requested. SRGs conducting the first level of review are composed primarily of nonfederal experts qualified by training or experience in particular scientific or technical fields, or authorities knowledgeable in the fields related to the applications under review. No more than one-fourth of the members of any SRG may be federal employees. SRGs may include public members with perspective on the public health impact of the research being considered.

The second level of peer review is performed by the national advisory council of the appropriate IC. National advisory councils are composed of scientific and public members chosen for their expertise, interest, or activity in matters related to a specific area of science, health, or disease. The vast majority of SRG-reviewed applications assigned to an IC go to the IC's Council,[42] which then recommends which applications should be considered for funding. 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.

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[41] http://grants.nih.gov/grants/peer_review_process.htm.

[42] 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.

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 that review process is important, but it is not the sole factor determining an IC's funding decision. Other considerations are portfolio balance, public health needs, programmatic relevance, IC priorities, requirements specified in congressional appropriations, and availability of funds.

Many ICs establish a *payline*, which is a percentile-based[43] funding cutoff point that is determined at the beginning of the fiscal year by balancing the projected number of applications assigned to an IC with the amount of funds that NIH and the IC expect to be available for such projects. Applications that score within the payline are most likely to be funded. For applications that are not percentiled, ICs typically make awards up to the funding limit set aside for that particular funding opportunity. However, advisory councils consider, evaluate, and make recommendations on applications that score both within and outside the payline and funding limit.

Additionally, 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 of 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.[44] NIH also monitors compliance with federal

[43] Percentile represents the relative position or rank (from 1 to 100) of each overall impact/priority score.
[44] 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.

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.

Intramural Research Program

The Intramural Research Program (IRP) is the internal research program of the NIH, known for its synergistic approach to biomedical science. Approximately 11 percent of NIH funds support research and training activities carried out by IRP scientists.

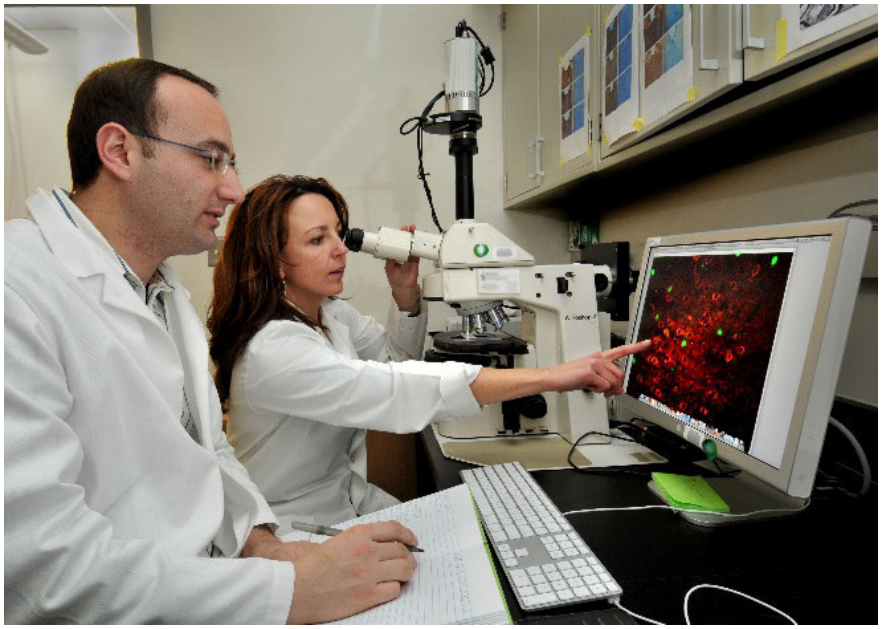

Figure 4. Dr. Jennifer Bossert reviews data imagery in IRP's group-neurobiology of Relapses Section. Credit: Unknown photographer.

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 also is 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 laboratories are located on NIH campuses in the Bethesda (including the NIH Clinical Center), 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 1,100 principal investigators lead intramural research projects that involve more than 6,000 trainees ranging from high school students to postdoctoral and clinical fellows.

Figure 5. Front entrance to the NIH Rocky Mountain Laboratories in Hamilton, Montana. Credit: NIAID.

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[45] 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 addition, at least every four years, an external expert Board of Scientific Counselors reviews the work of each tenured/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 five 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 more targeted outside reviews using external experts that make recommendations to enhance the laboratory and clinical research environment at the NIH. In one such

[45] 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.

review, a subcommittee of the Advisory Committee to the Director (ACD) examined the IRP in an effort to guide its long-term planning efforts, releasing its report in December 2014.[46] The 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. The report also provides a summary of research areas in which the IRP is perfectly poised to make major advances.

OIR is responsible for trans-NIH oversight and coordination of the IRP, human subject protections, animal welfare, 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. The IRP in 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 Sourcebook.

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 partnership with universities in the U.S. and abroad) to develop scientific and professional skills needed to become 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 clinical research takes place at teaching hospitals around the country and overseas. Approximately 1,600 studies, however, take place at the NIH Clinical Center in Bethesda, Maryland, at any given time. 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.

The CC is the nation's largest hospital devoted entirely to clinical research and is comprised of 200 patient beds and 93 day-hospital stations. Each year, the CC serves more than 10,000 new patients and supports more than 50,000 inpatient days and 95,000 outpatient visits. In addition to approximately 1,200 credentialed physicians, dentists, and postdoctoral researchers, it houses more than 600 nurses and 450 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 nearly 510,000 clinical research participants. Because the CC is a research facility, only patients with the precise kinds or stages of illness under investigation are admitted for treatment. There is 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.

[46] http://acd.od.nih.gov/reports/ACD-IRP-WG-report.pdf.

Figure 6. Aerial view of the Clinical Center (Building 10) on the NIH Campus in Bethesda, Maryland. Credit: NIH.

Though 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.

The CC continues to build on its proud history of tackling the world's toughest public health challenges. For example, the NIH CC has emerged at the forefront of addressing the Ebola crisis.[47] 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 identifying populations at increased risk, with the goal of developing novel preventive and therapeutic strategies to address human disease.

[47] https://clinicalcenter.nih.gov/ebola1.html.

Fostering Commitment to Science

New advances in the prevention, diagnosis, and treatment of disease depend on the creativity and insight of the best scientists. For these advances to continue, there must be a regular source of highly trained, well-equipped, and innovative investigators. This relies on a continuing pipeline of a talented and diverse research workforce. In addition, NIH must rely on a scientifically receptive public to ensure that research is moved into practice. For these reasons, NIH invests in the recruitment, training, and retention of its 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 research training and career development programs are designed to prepare new researchers to solve emerging problems in health. These programs aim to ensure that diverse pools of highly trained scientists are available in sufficient numbers and with appropriate expertise to generate new discoveries, take advantage of rapidly moving scientific developments, and bring science to bear on complex and evolving health care challenges. By sponsoring research training and career development programs in universities, teaching hospitals, NIH laboratories, and other research-intensive settings, NIH expects to ensure that trainees and newly trained investigators will be exposed to the latest research findings and techniques, and also will be positioned to respond to developing national and international public health needs. 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.

The task of assessing and predicting research personnel needs across the entire spectrum of biomedical health-related research is daunting. Aligning the requisite expertise with public health needs is complicated by the evolving nature of research, the time required for research training, the international nature of research, and the mobility of the global research workforce. Preparing for a career in research generally requires a commitment of 8 to 10 years or more, encompassing predoctoral and postdoctoral training and career development; in the meantime, science is advancing, new diseases are emerging, and existing diseases are becoming better understood, diagnosed, and prevented.

In determining how best to address the continuing need for biomedical and behavioral scientists, NIH is guided by regular analyses of the research workforce. NIH routinely evaluates the outcomes of its training programs by comparing the subsequent research involvement of students and postdoctoral scholars who participate in NIH research training with that of their counterparts who were trained through other sources. Beyond such agency-wide assessments, individual ICs determine the need for new scientific personnel in mission-specific research areas through targeted evaluations, input from extramural investigators, and guidance from their national advisory councils.

NIH offers a broad range of research training and career development opportunities through institutional training awards, individual fellowships, individual and institutional career development

awards, research education programs, workshops, research grants, and supplements to promote diversity or reentry into health-related research careers. Although its programs are largely directed toward graduate students and newly trained investigators, NIH offers a number of highly focused training and career development opportunities for individuals at other career stages, from college students to established scientists.

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:

- Funded Ruth L. Kirschstein NRSA and NLM *Institutional* Research Training Grants, FY 2014 and 2015
- Funded Ruth L. Kirschstein NRSA *Individual* Fellowship Awards, FY 2014 and 2015

Trans-NIH Programs and Initiatives

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. They are provided either through training grants (T awards), which are awarded to institutions to support a coordinated program 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. 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.

Through the NIH-wide program of NRSA institutional training grants and fellowships, NIH ICs supported more than 15,600 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every state in FY 2015. 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 63 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 fellowships provide recipients with valuable experience in initiating and testing their own research ideas before becoming full-fledged investigators.

Across NIH, NRSA training grants and fellowships help ensure the diversity of the research workforce by promoting research training opportunities for individuals 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 trainees 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,[48] NIH also provides graduate students from underrepresented groups with opportunities to pursue research training through individual fellowship awards. 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 a research career and who intend to pursue postgraduate education leading to a Ph.D., M.D./Ph.D., or other combined research degree.

The relative diversity of research training participants reflects NIH's commitment to cultivating a broad-based scientific workforce. For FY 2015 trainees and fellows who reported their race and ethnicity, 65.3 percent were White, 15.0 percent were Asian, 6.1 percent were African American, 10.2 percent were Hispanic, 0.5 percent were Native American, 0.2 percent were Native Hawaiian or Other Pacific Islanders, and 4.1 percent were multiracial. Nearly 52 percent of trainees and fellows in FY 2015 were women.

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.

Notable examples include the training grants and institutional career development awards in clinical and translational research that have been incorporated into the growing network of Clinical and Translational Science Awards (CTSAs)[49] administered by NCATS. Now active at more than 50 sites around the country, the CTSA program provides research training and career development opportunities in areas such as clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, behavioral science, and ethics to more than 750 NRSA trainees and new investigators annually. CTSA trainees are included in the NRSA data provided in Appendix E.

Additional trans-NIH training endeavors include the Common Fund's BD2K program and the NIH Blueprint for Neuroscience Research. The BD2K program, launched in 2012, supports formal research

[48] https://grants.nih.gov/grants/guide/pa-files/PA-14-148.html.
[49] http://www.ncats.nih.gov/ctsa.

training and career development programs, as well as short courses, research experiences, and the development of new curricula and other educational resources for the data sciences. NIH Blueprint for Neuroscience Research programs also are providing the next generation of scientists with extraordinary opportunities for training in integrated neuroscience. This cooperative effort between 17 ICs and Offices, underway since 2004, supports research education and training in computational neuroscience for undergraduates and graduate students, as well as targeted short courses in topics such as neurotherapeutics and the use of state-of-the art scientific tools and methods. For example, the Blueprint-supported Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (ENDURE) engages undergraduates from underrepresented groups in a two-year neuroscience research program during the academic and summer months, starting in sophomore or junior year, for an average of 1,700 research hours upon completion of the program.[50] As of FY 2015, 52 of 86 (60 percent) participants are in a graduate neuroscience program.

Another trans-NIH initiative is the Early Independence Awards.[51] These awards, supported by the Common Fund, provide newly trained scientists who have the intellect, scientific creativity, drive, and maturity to flourish independently with a chance to forgo the traditional period of postdoctoral training and pursue their own program of independent research. To date, Early Independence awardees have lived up to their exceptionally high potential, publishing numerous high-impact papers, uncovering groundbreaking scientific insights, and earning recognition from the *Forbes* "30 Under 30" and the Presidential Early Career Awards for Scientists and Engineers.

NIH recognizes that traditional research-intensive positions are not the only means by which newly trained investigators can contribute meaningfully to the biomedical research enterprise. The Common Fund's strengthening of the Biomedical Research Workforce program[52] aims to enhance training opportunities for early-career scientists to prepare them for a variety of career options in biomedical research through a series of Broadening Experiences in Scientific Training (BEST) awards, of which the second cohort was awarded in FY 2014. Awardee institutions collaborate with nonacademic partners to expand training opportunities for early career scientists to prepare them for entry into the dynamic biomedical workforce landscape. Also in FY 2014, the BEST awardees launched a comprehensive website where trainees, faculty, and administrators can find resources on preparing trainees for a wealth of different career paths.[53] Additionally, a rigorous evaluation of novel training approaches is underway to determine which approaches are most effective and in what contexts. The BEST website will enable wide dissemination of proven approaches throughout the biomedical research community.

As mentioned previously, the DPC is one component of the trans-NIH strategy used to attract and retain talented individuals from all sectors of the population in biomedical research.[54] Supported by the Common Fund, managed by NIGMS, and launched in FY 2014, this program consists of three highly integrated components: the BUILD initiative, which is a set of experimental training awards designed to

[50] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-14-010.html.
[51] http://commonfund.nih.gov/earlyindependence.
[52] http://commonfund.nih.gov/workforce/index.
[53] http://www.nihbest.org/.
[54] http://commonfund.nih.gov/diversity/index.

learn how to attract students from diverse backgrounds into the training pipeline and to encourage their persistence in biomedical research careers; a National Research Mentoring Network, which is developing novel mentoring strategies, establishing standards and training for mentors, and developing a diverse network of mentors and mentees across the country; and the Coordination and Evaluation Center, which works across all components and awardee institutions to determine what works and for whom and disseminates lessons learned to the broad biomedical research training community.

Other offices within the NIH OD are engaged in coordinating trans-NIH training and career development initiatives. In FY 2014 and 2015, ORWH continued to support the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program, a mentored career development program for junior faculty interested in careers in women's health. The current round of BIRCWH programs is supported by NICHD, NCI, NIA, NIAMS, NIDA, NIAID, OAR, and NIMH. ORWH and NIDA provide programmatic oversight for these BIRCWH programs, and NICHD provides the grants-management oversight.[55]

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

To gain a better understanding of how graduate students and postdoctoral fellows contribute to research projects, in FY 2010, NIH asked investigators to identify all research project personnel on their annual progress reports. In 2013, NIH expanded that effort to collect information on the educational and demographic backgrounds of all students and postdoctorates working on NIH research projects. With the resulting data, NIH is now better able to determine the size and characteristics of the workforce associated with its grants, and to understand the role that students and postdoctorates play in that workforce.[56]

IC Programs and Initiatives

Because each NIH IC has its own research mission, individual ICs are responsible for determining how the national workforce needs apply to their specific scientific fields, selecting individuals and institutions for NRSAs or other research training awards to meet the needs identified, and reviewing annual progress toward building or enhancing capacity in the research workforce. Areas targeted for research training initiatives reflect the full array of NIH interests, from basic research training in biology, chemistry, and biomedical engineering to clinical and translational research training in fields like cancer, infectious diseases, diabetes, cardiovascular diseases, and aging.

To ensure a supply of investigators attuned to the challenges of both research and patient care, ICs also make awards for M.D./Ph.D. and other types of dual-degree training. The oldest and largest of the dual-

[55] https://orwh.od.nih.gov/career/mentored/bircwh/.
[56] http://www.fasebj.org/content/30/3/1023.full.pdf+html.

degree programs is the NIGMS Medical Scientist Training Program (MSTP),[57] which supports exceptional students pursuing an integrated program of graduate training in the biomedical sciences and clinical medicine. In 2014, the MSTP marked its 50th anniversary of supporting students working toward M.D./Ph.Ds. Examples of research by MSTP-funded trainees include studies that synthesized and characterized novel potential therapeutics for bone tissue engineering,[58] developed new treatment strategies for HIV-infection,[59] and pioneered approaches for detecting genetic mutations leading to neurodevelopmental disease.[60]

Reflecting the FIC mission to foster global health research and build research capacity in low- and middle-income countries, FIC institutional training grants (D43s) and research education programs (R25s) differ from those offered by the NRSA program (see above) or by NLM (see below). FIC grants allow a broader range of participants and emphasizing the development of institutional partnerships and collaborations between U.S. and international universities and scientists. Most FIC programs target individuals from low- and middle-income nations, but several programs provide opportunities to U.S. students and postdoctoral fellows interested in global health research. For example, FIC's Global Health Program for Fellows and Scholars brings together early-stage investigators from the U.S. and low- and middle-income countries and provides supportive mentorship, research opportunities, and a collaborative research environment to enhance their global health research expertise and their careers. To date, this program has provided training to more than 4,900 students and postdoctorates at approximately 80 research sites in 27 low- and middle-income countries.

Figure 7. Jessica Manning, M.D., conducts malaria vaccine research as a Fogarty International Clinical Research Scholar in Mali. Credit: Jessica Manning.

[57] https://www.nigms.nih.gov/Training/InstPredoc/Pages/PredocOverview-MSTP.aspx.
[58] Watson BM, et al. *Biomacromolecules* 2014;15(5):1788-96. PMID: 24758298.
[59] Halper-Stromberg A, et al. Cell 2014;158(5):989-99. PMID: 25131989.
[60] Jamuar SS, et al., *N Engl J Med* 2014;371(8):733-43. PMID: 25140959.

FIC also invests in a variety of research training and education programs aimed at fostering research capacity in developing countries. Through its Medical Education Partnership Initiative, for example, FIC is working to increase the quality, quantity, and retention of medical faculty and physicians with research skills in sub-Saharan Africa, and foster relationships with public sector partners that promote sustainable research capacity. The Global Health Research and Research Training eCapacity Initiative program supports innovative research education programs to teach researchers at low- and middle-income country (LMIC) institutions the knowledge and skills necessary to incorporate Information and Communication Technology (ICT) into global health research and research training. The FIC HIV Research Training Program instructs researchers from LMIC institutions in how to conduct research on evolving HIV-related epidemics in their countries and to compete independently for research funding. Research training supports topics such as HIV prevention, HIV-TB co-infection, and other comorbidities of HIV infection and treatment.

NLM's research training portfolio generally parallels the structure and requirements of the NRSA program and reflects NLM's unique role as the primary federal sponsor of biomedical informatics research and training. NLM prepares the next generation of informatics researchers and health information specialists through institutional research training grants (T15s)[61] that support graduate and postdoctoral training in areas such as health care informatics, translational bioinformatics, clinical research informatics, and public health informatics, as well as specialized areas such as imaging and dental informatics. NLM training programs have been very effective in advancing biomedical informatics research, as evidenced by publication and citation records in relevant scientific literature. In FY 2015, for example, more than 25 percent of cited articles acknowledging an NLM grant identified an NLM training grant as the source of support. Fourteen Principal Investigators, together with supporting faculty and administrative staff, and more than 200 trainees were supported during FY 2014 and 2015.

NLM also offers a post-master's degree fellowship on the NIH campus designed to provide librarians with a broad foundation in health sciences information services and to prepare them for leadership roles in health science libraries and in health services research.[62] Nine fellows participated in the fellowship in FY 2014 and 2015. Efforts to recruit fellows from underrepresented groups have been successful in attracting diverse groups of fellows to the program.

In a similar vein, other ICs provide specialized training and career development opportunities in areas reflecting their respective scientific missions. For example, NHLBI has taken the lead in building a coalition of ICs to support an institutional career development program in emergency care research.[63] This program will conclude in 2017, having trained more than 30 clinician-scientists. Many of the program's graduates have gone on to receive NHLBI Career Development Awards, and one is now an R01-funded investigator. NIDDK plays a similar role in fostering the research career development of pediatric endocrinologists.[64] The Career Development Program in Diabetes Research for Pediatric

[61] http://www.nlm.nih.gov/ep/GrantTrainInstitute.html.
[62] https://www.nlm.nih.gov/about/training/associate/.
[63] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-11-011.html.
[64] http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-006.html.

Endocrinologists provides an opportunity for research career development after the clinical fellowship years to facilitate the transition to a fully trained independent investigator, building upon the foundation of current basic and clinical knowledge and developing new approaches toward the treatment, prevention, and cure of pediatric diabetes.

NCI has several initiatives focused on fostering the career development of researchers in the field of cancer research. The Cancer Clinical Investigator Team Leadership Awards (CCITLA) provide two years of funding to exceptional mid-level clinical investigators at NCI-designated Cancer Centers who lead NCI-sponsored clinical trials but are not principal investigators.[65,66] The NCI Outstanding Investigator Award (OIA) supports investigators with outstanding records of productivity in cancer research by providing extended funding stability and encouraging investigators to continue or embark on projects of unusual potential in cancer research. The OIA provides substantial time for funded investigators to take greater risks and be more adventurous in their research.[67]

Many ICs have developed initiatives specifically focused on supporting early career investigators. The NIDA Avenir Award Program supports early-stage investigators who may lack the preliminary data required for an R01 application, but who propose highly innovative and impactful research and who show promise of being tomorrow's leaders in the field of addiction science. In June 2015, NIDA announced the recipients of two newly developed Avenir Award Programs, one for HIV/AIDS research and the other for genetics or epigenetics studies.[68]

Launched in February 2015, the NIAMS-led Supplements to Advance Research (STAR) award program provides additional support to early-stage investigators who have renewed their first NIAMS-funded R01 award to pursue innovative and high-risk research within the broader scope of a current NIAMS-funded, peer-reviewed research project. The award also helps investigators to expand a single, structured research project into a broader, multi-faceted research program.[69]

The NIDCR Dentist Scientist Pathway to Independence Award (K99/R00) is designed to increase and maintain a strong cohort of independent dual-degree dentist-scientists by providing research support to assist these individuals in launching independent research careers. One of NIDCR's dentist-scientist trainees recently discovered two distinct types of marrow adipose cells in bone that regulate bone metabolism and could provide potential therapeutic targets for osteoporosis.[70,71] Similarly, NIMH issued the NIMH Administrative Supplement Program to Enable Continuity of Research Experiences of M.D./Ph.D.s during Clinical Training.[72] This program supports advanced research opportunities for

[65] https://www.cancer.gov/about-nci/organization/ccct/funding/ccitla/
[66] http://www.cancer.gov/about-nci/organization/ccct/funding/ccitla/2009-2015-ccitla-recipients.pdf.
[67] Relevant PMIDs, program websites, or web links to press releases: http://www.cancer.gov/grants-training/grants/funding-opportunities/oia.
[68] https://www.drugabuse.gov/news-events/news-releases/2015/06/nida-announces-new-awards-early-stage-investigators.
[69] http://www.niams.nih.gov/news_and_events/Announcements/2015/STAR_awardees.asp.
[70] http://www.eurekalert.org/pub_releases/2015-08/uomh-osd080615.php.
[71] Scheller EL, et al. *Nat Commun* 2015;6:7808. PMID: 26245716.
[72] https://grants.nih.gov/grants/guide/pa-files/PA-14-263.html.

individuals holding M.D./Ph.D. degrees who are early in their research careers, with the goal of helping these individuals transition efficiently and effectively from clinical training to the next stage of their research careers. This supplemental award provides focused, protected research time for eligible individuals during residency and/or clinical fellowship.

Several ICs run short, intensive training courses to help develop and prepare researchers in their areas of focus. For example, the NINR Methodologies Boot Camp is a one-week intensive research training course at the NIH Campus sponsored by NINR and run by the Foundation for Advanced Education in the Sciences (FAES). In 2014 and 2015, the Boot Camp focused on Big Data Methodologies.[73] NINR also sponsors the Summer Genetics Institute (SGI), a tuition-free, one-month intensive research training program on the main NIH Campus that provides participants with a foundation in molecular genetics appropriate for use in research and clinical practice. The program features lectures and hands-on laboratory training, and seeks both to increase the research capability among graduate students and faculty and to develop and expand clinical practice in genetics among clinicians.[74]

In FY 2014 and 2015, OBSSR held Summer Research Training Institutes to support the application of behavioral and social science perspectives in biomedical research.[75] These training institutes gave researchers residential, immersive settings for their work and projects, as well as mentoring and networking opportunities. Institutes included Randomized Clinical Trials,[76] mHealth,[77] and Dissemination and Implementation Research.[78] In 2015, OBSSR also hosted a day-long event on Defining Your Career in Behavioral and Social Sciences.[79] This was the most popular event of OBSSR's 20th Anniversary Celebration and led to the development of additional events focusing on early-stage investigators.

Other offices within the NIH OD are engaged in the training and career development of researchers. Initiated in FY 2014, the Center for Evaluation and Coordination of Training and Research (CECTR), part of the ODP Tobacco Regulatory Science Program, serves as a national resource in tobacco regulatory science, supports and conducts evaluation of the scientific programs funded by the FDA and Center for Tobacco Products, and facilitates coordination and communication of research and scientific training within those programs. Through leadership, evaluation, coordination, and facilitation of collaborative efforts, CECTR seeks to accelerate the advancement of science relevant to the *Family Smoking Prevention and Tobacco Control Act* (FSPTCA).

Individual ICs place continued emphasis on the recruitment, retention, and graduation of individuals from diverse backgrounds, including underrepresented groups. For example, NIGMS manages the Institutional Development Award (IDeA) program, which aims to broaden the geographic distribution of

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[73] http://www.ninr.nih.gov/training/trainingopportunitiesintramural/bootcamp#.Vz9WBPkrJD8.
[74] http://www.ninr.nih.gov/training/trainingopportunitiesintramural/summergeneticsinstitute#.Vz9V6fkrJD8.
[75] https://obssr.od.nih.gov/training/training-institutes/.
[76] https://obssr-archive.od.nih.gov/training_and_education/annual_Randomized_Cliical_Trials_course/RCT_info.aspx#dat.
[77] https://md2k.org/events/traininginstitute/agenda/.
[78] https://obssr.od.nih.gov/training/training-institutes/training-institute-on-dissemination-and-implementation-research-tidirh/.
[79] https://obssr.od.nih.gov/events/obssr-20th-anniversary/.

NIH funding for biomedical research throughout the U.S. The IDeA program fosters health-related research, enhances the competitiveness of researchers in states in which NIH support historically has been low, and serves unique populations such as rural and underserved communities in these states. The IDeA program strengthens the research capabilities of biomedical faculty and their institutions and provides access to biomedical resources for promising undergraduate students.[80] In addition, the NIGMS Support of Competitive Research (SCORE) developmental program that seeks to increase research competitiveness of faculty at institutions that have historically focused on serving students from underrepresented groups.[81]

In 2014, NHLBI launched an initiative to increase the number of highly trained investigators from diverse backgrounds who are underrepresented in NHLBI-related research. The program provides salary and research support for three to five years to non-tenured science faculty and scientists, and physicians with some research experience who need guided coursework and supervised laboratory experiences. The program aims to enable these researchers to receive the training necessary to launch independent research careers.[82] The Program to Increase Diversity Among Individuals Engaged in Health-Related Research (PRIDE) is an NHLBI diversity-targeted research, education, and mentoring program for junior faculty from backgrounds designated as underrepresented by the National Science Foundation. It has been operational for a decade and has trained 204 junior faculty who have since collectively garnered 58 grants, including 8 R01s and 21 K awards, and have published 1,837 papers. The PRIDE program is on track to train more than 200 additional junior faculty by the end of FY 2018.[83,84]

In September 2015, NIDA awarded two contracts to support the career and research development of American Indian/Alaska Native (AI/AN) scholars dedicated to pursuing substance use and addiction research within AI/AN communities. Contracts were awarded to Colorado University Health Science Center and the University of Washington. These mentoring programs are designed to improve AI/AN health and eliminate substance use-related health disparities.[85]

NIDCR research training directors attend national scientific conferences to advise students and scientists at all career levels about research training and career development opportunities. In FY 2014 and 2015, the NIDCR Committee on Diversity and Inclusion increased the breadth of outreach by developing digital media channels. The committee initiated a LinkedIn presence to highlight career development opportunities, began using the *@NIDCR* Twitter channel for this communication goal, and created the *Diversity & NIDCR* portal to encourage individuals from underrepresented racial and ethnic groups, individuals with disabilities, and women to apply for NIDCR career development support.[86]

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[80] https://www.nigms.nih.gov/Research/CRCB/IDeA/Pages/default.aspx.
[81] https://www.nigms.nih.gov/research/crcb/SCORE/Pages/default.aspx
[82] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-006.html.
[83] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-021.html.
[84] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-022.html.
[85] https://www.drugabuse.gov/about-nida/organization/offices/office-nida-director-od/odhd/odhd-research-training-programs#summer.
[86] http://www.nidcr.nih.gov/careersandtraining/diversity/diversity-and-nidcr.htm.

Several ICs have developed initiatives to support research experiences for undergraduate students from underrepresented populations who are considering pursuing a research career. The NIGMS Maximizing Access to Research Careers (MARC) U-STAR awards[87] provide support for undergraduate students who are from underrepresented backgrounds in the biomedical sciences to improve their preparation for high-caliber graduate training at the Ph.D. level. Research that MARC trainees led and contributed to include studies on elucidating the structures of cellular receptors,[88] identifying mechanisms of muscle fiber differentiation,[89] and uncovering novel factors that contribute to the etiology of language disorders in children with Down syndrome.[90]

The NIDA Summer Research Internship Program introduces high school and undergraduate students from underrepresented populations to addiction research through internships with NIDA-funded scientists at universities across the U.S. The experience may include laboratory experiments, formal courses, data collection activities, data analysis, patient recruitment, patient interviews, manuscript preparation, literature reviews, and library research. Internships include a paid eight-week, intensive, hands-on addiction research experience that provides students with the opportunity to gain an understanding of the research process. Since the program's inception in 1997, more than 930 students have gained valuable addiction research experience; some of these students have pursued a career in addiction research.[91]

The NIDDK Short-Term Research Experience Program for Underrepresented Persons (STEP-UP) provides hands-on summer research experience for high school and college students interested in exploring research careers in the biomedical, behavioral, clinical, and social sciences, with an emphasis on diabetes, endocrinology and metabolic diseases; digestive diseases and nutrition; and kidney, urologic and hematologic diseases. STEP-UP seeks to increase the participation in biomedical sciences of students from backgrounds underrepresented in biomedical research, including individuals from disadvantaged backgrounds, individuals from underrepresented racial and ethnic groups, and individuals with disabilities.[92]

Challenge competitions[93] can be a creative mechanism to support training and career development. Since 2012, NIBIB has held annual Design by Biomedical Undergraduate Teams (DEBUT) Challenges for undergraduate students to develop innovative solutions to unmet health and clinical problems. These challenges offer monetary prizes, which are incentives for the next generation of innovators; past

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[87] https://www.nigms.nih.gov/Training/MARC/Pages/USTARAwards.aspx.
[88] Wilding TJ, et al. *Nat Commun* 2014;5:3349. PMID: 24561802.
[89] Chechenova MB, et al. *PLoS One* 2015;10(12):e0144615. PMID: 26641463.
[90] Edgin JO, et al. *Child Dev* 2015;86(6):1984-98. PMID: 26435268.
[91] https://www.drugabuse.gov/about-nida/organization/offices/office-nida-director-od/odhd/odhd-research-training-programs#summer.
[92] https://www.niddk.nih.gov/research-funding/research-programs/diversity-programs/research-training-opportunities-students/short-term-research-experience-underrepresented-persons-step-up.
[93] Challenge and prize competitions are one path that Federal agencies take to drive innovation and solve mission-centric problems. With a challenge competition, a "seeker" poses a problem or question to the public and "solvers" respond and submit solutions. An agency only awards those solutions that meet the criteria and are chosen as winners. More information is available at https://www.challenge.gov/.

winners have gone on to patent their devices and create start-up companies. Winning projects in 2014[94] and 2015[95] are presented on the NIBIB website.

Extramural Programs and Progress: Career Development

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)[96] 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, while 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[97] accelerates the transition from mentored to independent research by providing a bridging mechanism of an initial mentored period of one to two 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 that they can focus intensively on their research and mentor new investigators.

Training and Career Development Program Evaluations and Assessments

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.

Evaluations of the outcomes of NRSA research training have routinely found that graduate students participating in NRSA programs complete their degrees in a shorter timeframe, are more likely to pursue research careers, and have greater subsequent success in research compared with students not

[94] https://www.nibib.nih.gov/training-careers/undergraduate-graduate/design-biomedical-undergraduate-teams-debut-challenge/2014-design-biomedical-undergraduate-teams-debut-challenge-winners.
[95] https://www.nibib.nih.gov/training-careers/undergraduate-graduate/design-biomedical-undergraduate-teams-debut-challenge/2015-design-biomedical-undergraduate-teams-debut-challenge-winners#overlay-context=user.
[96] http://grants.nih.gov/training/careerdevelopmentawards.htm.
[97] http://grants1.nih.gov/grants/guide/pa-files/PA-11-197.html.

participating in NRSA programs.[98] Similarly, assessments of NRSA postdoctoral training have found that NRSA postdoctoral fellows are more likely to successfully pursue research careers. A 2015 analysis found that nearly 30 percent of former NRSA postdoctoral fellows received major NIH research grant funding within 10 years of their fellowship training, whereas fewer than 15 percent of other postdoctoral fellows did so.

NIH also has evaluated its three most widely used types of mentored career development awards: K01, K08, and K23. Comparing similar groups of funded and unfunded applicants, NIH found that those who received a career development award were more likely to remain in research; publish their research findings; apply for and receive major NIH research grants; and, for those whose careers were tracked over sufficient time, apply for and receive a grant renewal.[99] Although all investigators receiving these career development awards fared well, having a mentored career development experience had the greatest impact on M.D.s and M.D./Ph.Ds.

In 2015, NIH completed a preliminary assessment of one of its newest career development programs, the K99/R00 Pathway to Independence Award. Intended to help early-stage investigators transition to faculty positions and establish themselves as independent investigators more quickly, preliminary findings suggest that the program is achieving its goals. Among K99/R00 awardees who have gone on to obtain subsequent research support from NIH, the average age at which they received a major R01 research grant was 39—three years less than the average age at which new investigators reached that milestone at the time the Pathway to Independence program was established in 2006.

Government Performance and Results Act (GPRA) Measures

Every year, NIH reports on NRSA research training outcomes and program management using two GPRA measures. With these measures, NIH seeks to assess the quality of its programs and determine whether substantial numbers of trainees and fellows are retained in research careers by comparing the proportion of former NRSA trainees and fellows who apply for and receive NIH research grant support with that of their peers. Subsequent NIH support 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, NIH generally has met these GPRA measures because NRSA trainees and fellows consistently outperform their counterparts.

IC Training Evaluations

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, in 2015 NICHD undertook a comprehensive evaluation of its research training and career development programs. As a result of that assessment, the Institute rebalanced its training portfolio to place a greater emphasis on individual rather than institutional career development

[98] https://researchtraining.nih.gov/resources/data-outcomes-and-evaluations.
[99] http://grants.nih.gov/training/K_Awards_Evaluation_FinalReport_20110901.pdf.

awards.[100] In recent years, NIGMS also has assessed the career outcomes of trainees in its Maximizing Access to Research Careers (MARC) program and the postdoctoral scholars participating in its Institutional Research and Academic Career Development Awards (IRACDA) career development program.[101]

Coordination and Oversight by the NIH Office of Extramural Research

OER partners with ICs to coordinate and monitor awards for research training and career development across NIH. With active input from the ICs, OER establishes and implements policies and guidelines for each program; determines broad national needs for basic biomedical, behavioral, and clinical research personnel; coordinates NIH-wide evaluations; develops trans-NIH research initiatives in which NIH ICs participate; and develops and maintains information systems to enhance program efficiencies. OER convenes monthly meetings of the NIH Training Advisory Committee to provide an agency wide forum to identify and discuss issues related to research training and to provide opportunities to coordinate activities pertinent to the review, administration, management, and evaluation of training grants and fellowships.

Intramural Activities

The NIH intramural program provides opportunities for students, postdoctoral scholars, and clinicians to gain research experience within the more than 1,100 NIH intramural laboratories. A multifaceted array of programs provides a vibrant, scholarly environment and ensures strong research training experiences for future investigators and the continued professional development of intramural scientists.

Among the intramural program's offerings are summer internships for high school, college, and graduate students. Recent college graduates who plan to apply to graduate or professional school also can spend a year engaged in biomedical research working side by side with NIH scientists. Current graduate students can spend a summer or a year as fellows engaged in biomedical research at NIH. The Graduate Partnerships Program[102] enables students to pursue research toward their degrees at NIH in partnership with a participating academic institution. By linking academic environments with the breadth and depth of research at NIH, the Graduate Partnerships Program offers a unique graduate experience. Similarly, the Medical Research Scholars Program[103] provides research-oriented medical, dental, and veterinary students an opportunity to engage in a mentored clinical or translational research project on the NIH campus.

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[100] https://www.nichd.nih.gov/training/extramural/Documents/NICHD_training_review.pdf#search=training evaluation.
[101] https://www.nigms.nih.gov/about/council/minutes/Pages/may19-20_2016.aspx.
[102] https://www.training.nih.gov/programs/gpp.
[103] http://www.cc.nih.gov/training/mrsp/index.html.

Figure 8. NIH Medical Research Scholars Posed in the lab. Credit: NIH CC.

Training opportunities continue when scholars gain their graduate degrees. Year-round, NIH intramural laboratories employ fellows from the U.S. and abroad, creating a thriving, multidisciplinary intramural research community. The Postdoctoral Intramural Research Training Award[104] allows recent doctoral degree recipients who are U.S. citizens or permanent residents to enhance their research skills in the NIH intramural environment. Trainees pursue both basic and clinical research. A parallel program, Visiting Fellowships, serves foreign national doctoral-level scientists. NIGMS has its own small but unique intramural research training program, the NIGMS Postdoctoral Research Associate (PRAT) Program, which enables postdoctoral trainees to pursue research in one of the NIH laboratories. PRAT is a three-year program placing special emphasis on training fellows in all areas supported by NIGMS.[105]

For clinicians, NIH offers opportunities for residency and subspecialty training, including accredited graduate medical education programs. (For program completion data, see Appendix E.) These graduate medical education programs enable research-oriented clinicians to weave research experience and training into their post-medical school training. Other programs for clinicians include a clinical research fellowship for dentists interested in academic careers, which combines hands-on experience in a clinical or translational research project with formal training in research methodologies and skills such as grant-writing.[106]

In recent years, NIH's IRP has increasingly focused on helping graduate students and postdoctoral fellows develop their career skills. To ensure that intramural trainees and fellows can advance in their careers, NIH offers courses in scientific writing, grant writing, and presentation and teaching skills. In

[104] https://www.training.nih.gov/programs/postdoc_irp.
[105] https://www.nigms.nih.gov/Training/Pages/PRAT.aspx.
[106] http://www.nidcr.nih.gov/CareersAndTraining/Fellowships/PostdoctoralScientists/NIDCRClinicalResearchFellowship/.

addition, intramural trainees and fellows—indeed, all members of the NIH community—benefit from access to a wealth of NIH courses, seminars, and science career resources, providing information on both traditional and nontraditional science careers.

To help better prepare the trainees at NIH for possible careers in translational science, the NIH Office of Intramural Training and Education and NCATS have partnered to create the Translational Science Training Program (TSTP). The TSTP is an intensive two- to three-day training program that introduces NIH postdoctoral trainees and graduate students to the science and operation of turning basic research discoveries into a medical therapeutic, device, or diagnostic, and also exposes them to the variety of career options in translational science. Through a combination of classroom teaching from practicing experts in the various disciplines of translation and small-group interactions with preclinical development teams, participants in the TSTP gain knowledge that will aid them in obtaining a career in translational science and building a network to make the transition to the field.[107,108]

The CC also provides a robust array of training resources for researchers, including the clinical research curriculum comprised of the *Introduction to the Principles of Practice of Clinical Research (IPPCR)*, *Principles of Clinical Pharmacology*, and *Ethical and Regulatory Aspects of Clinical Research*. The CC serves as the designated sponsoring institution providing administrative and curricular oversight for 18 medical or surgical graduate education training programs accredited by the Accreditation Council for Graduate Medical Education, a private nongovernment organization responsible for the accreditation of approximately 700 sponsoring institutions and 9,600 residency/clinical fellowship training programs nationally.

Loan Repayment Programs

The NIH Loan Repayment Programs[109] are a vital component of our nation's efforts to attract eligible doctoral-level professionals to research careers in fields of special importance, including clinical, pediatric, health disparities, contraception and infertility, and AIDS research. To encourage qualified scientists to pursue research in these critical areas, the Loan Repayment Programs provide financial assistance for educational debt in exchange for a one- to three-year research commitment, depending on the program. More than 1,300 program participants each year receive up to $35,000 annually in loan repayment and fulfill their commitments by conducting research in nonprofit, university, or government settings.

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. NIH funds a number of science education and literacy activities from elementary school through college. These programs support curriculum

[107] https://ncats.nih.gov/newsletters/vol04-iss03/mar2015.html#translate.
[108] https://ncats.nih.gov/enews/issues/vol05-iss05/ncats-hosts-nih-training-program.
[109] http://www.lrp.nih.gov/index.aspx.

development, mentoring, outreach, and research experiences designed to recruit individuals with specific backgrounds to research careers or to increase the diversity of the biomedical workforce.

NIH's Science Education Partnership Award (SEPA) program enables researchers, educators, and community groups to share their knowledge, expertise, and enthusiasm about health and science research with pre-kindergarten to grade 12 students, teachers, and the general public. SEPA-funded classroom- and museum-based projects generate resources, including hands-on and problem-based curricula, interactive health exhibits, films, afterschool and summer student internships, and professional development opportunities for teachers. The SEPA website is maintained by the SEPA community and provides universal access to educational resources, teacher training, health-based museum exhibits, and evaluation models that are developed via these SEPA-funded projects.[110]

NIH also organizes several large-scale events to improve science literacy across the nation, and often beyond. National DNA Day is a unique day when students, teachers, and the public can learn more about genetics and genomics. The day commemorates the April 2003 completion of the Human Genome Project and the 1953 discovery of DNA's double helix. Each year, NHGRI celebrates DNA Day with events to engage teachers in genomics education. DNA Day 2015 activities included the launch of two new resources for use in the classroom: (1) an inquiry-based lesson plan on human identity, designed to raise awareness about career opportunities in genomics, emphasize the importance of multidisciplinary collaboration for scientific discoveries, and address common misconceptions in genetics and genomics; and (2) an online interactive program called *What Do You Think*, which presents a series of challenging and engaging ethical questions about genetics and genomics research, allowing users to probe issues about genomics and health, research, identity, privacy, testing in children, discrimination, and societal applications.[111]

Brain Awareness Week, celebrated annually in March, is an annual global public outreach partnership of government agencies, universities, hospitals, patient advocacy groups, scientific societies, service organizations, and schools. Its purpose is to increase public awareness of the progress and benefits of brain research. NIMH and NINDS colead NIH Brain Awareness events in collaboration with other NIH Institutes including NIA, NIDA, NIAAA, NIDCD, NCI, NEI, and NICHD. NIMH celebrates with 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.[112,113]

National Drugs and Alcohol Chat Day provides students the opportunity to ask leading researchers questions about drug use, abuse, and addiction. Top scientists from NIDA, NIAAA, and FDA go live online to answer questions about drugs and their impact on the teen brain and body.[114]

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[110] http://www.nihsepa.org.
[111] https://www.genome.gov/10506367/national-dna-day/.
[112] http://www.nimh.nih.gov/about/director/2014/brain-awareness.shtml.
[113] http://www.nimh.nih.gov/about/director/2015/brain-awareness.shtml.
[114] https://www.drugabuse.gov/news-events/public-education-projects/drugs-alcohol-chat-day.

NIH takes an active role in pre-college (K–12) science education and in science literacy activities. These activities aim to improve the science knowledge and skills of students, attract young people to biomedical and behavioral science careers, lay the groundwork for advanced study, enhance public understanding of health science, and empower the public as consumers of science and health information. Changes to these programs continue to adapt to the current needs.

Curriculum supplements—ready-to-use, interactive teaching units—are one of NIH's important and effective science education efforts. Crafted through a unique collaboration of NIH scientists, teachers, and expert curriculum developers, the supplements are aligned with state education standards and are consistent with the National Science Education Standards. NIH has shipped more than 513,000 curriculum supplements upon request to K–12 educators across the nation. Topics covered include *The Science of Healthy Behaviors*, *Cell Biology and Cancer*, *The Brain: Understanding Neurobiology through the Study of Addiction*, *Exploring Bioethics*, *Evolution and Medicine* for high school biology classes, and *Rare Diseases and Scientific Inquiry* for middle schools.[115]

NIDA and Scholastic Inc. have partnered to create *Heads Up: Real News About Drugs and Your Body*, a science-based education series that provides teachers and students innovative materials about the effects of drug use on the brain and body. New materials, including teen articles, classroom lessons, and student worksheets, are created and distributed every school year through Scholastic's in-school magazines, posters and web-only materials.[116]

At the high school and middle school levels, NLM supports the *Mentoring In Medicine (MIM) Science and Health Career Exploration* program, which provides afterschool instruction to enrich the biology curriculum and encourage enrollment in higher education programs leading to degrees in medicine, allied health professions, and medical librarianship. Principals, science teachers, and guidance counselors from participating schools oversee 40 sessions of biology instruction in 12 organ systems, taught by visiting health professionals/mentors over a two-year period. Over the past five years, the program has exposed more than 800 minority students to healthcare career instruction. Program evaluations demonstrate continued impressive gains in health care knowledge. In addition to reaching seven public and charter high schools in New York City, in FY 2014, the program was expanded to include three schools in the Washington, D.C., area, with curriculum modifications to include middle school students.[117]

[115] These curriculum supplements are free to teachers and may be ordered at: http://science.education.nih.gov/supplements.
[116] https://www.drugabuse.gov/news-events/public-education-projects/nida-scholastic-heads-up.
[117] Holden L, et al. *Inf Serv Use* 2015;35(1-2):141-160. PMID: 26316659.

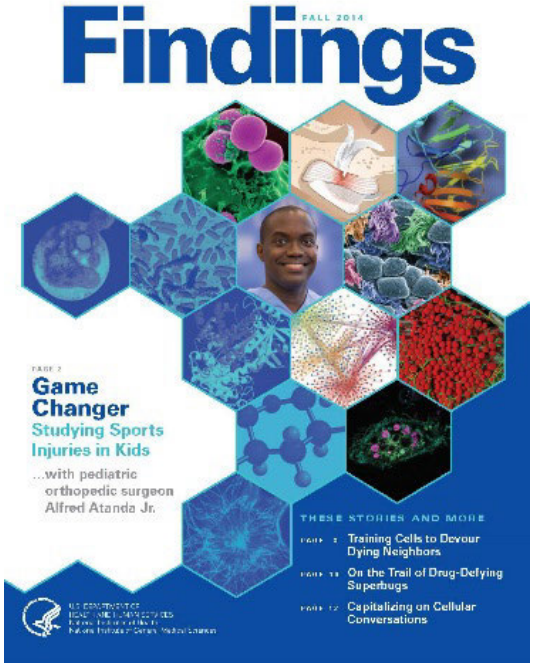

Figure 9. The *Findings* magazine showcases diverse scientists who do cutting-edge research and lead interesting lives. Each issue also contains brief research highlights, a puzzle or other activity, and online extras. Credit: NIGMS.

Other ICs have initiatives to encourage students to pursue education and careers in science, technology, engineering, and mathematics (STEM) areas. For example, *Findings*, a semiannual magazine produced by NIGMS, targets high school and early college students (Figure 9). It describes the excitement of cutting-edge research, the interesting people who pursue science careers, and the enjoyment they get from this work.[118] A companion website offers videos, podcasts, and interactive games expanding on the printed material. NIH also offers topical publications and school resources, such as slide kits, online quizzes, and science puzzles that are used by teachers across the country to augment textbooks and enrich the classroom experience. Subject areas include cell biology, genetics, structural biology, chemistry, pharmacology, and computational biology. Classroom posters linked to selected publications also promote interest in science and research careers and continue to be tremendously popular.

NIH also works to improve science literacy in school-age children by encouraging participation in science through various outreach events, such as the NIDA Science Fair Award for Addiction Science. Part of the Intel International Science and Engineering Fair (ISEF), the world's largest science competition for high school students, the Addiction Science Award is given by NIDA to three exemplary projects on the topic of addiction science. Addiction Science winners are announced at a special awards ceremony at the Fair and are invited to present their projects at NIH in Bethesda, Maryland.[119]

Because NIH fosters many initiatives to increase science literacy across all age ranges, different ICs focus on educating the public on scientific topics under their purview. For example, as the technology institute

[118] https://publications.nigms.nih.gov/findings/.
[119] https://www.drugabuse.gov/news-events/public-education-projects/nida-science-fair-award-addiction-science.

at the NIH, NIBIB has created several short videos as part of the *60 Seconds of Science* series that explain medical imaging tests in plain language. These videos include *How Ultrasound Works*,[120] *How Do X-rays Work?*,[121] and *What are Quantum Dots?*[122] NIBIB also developed the *Want to be a Bioengineer?* application for iOS and Android, which prompts students and adults to explore the types of research conducted by bioengineers. The game introduces users to real-life examples of how bioengineers improve people's lives, from helping paralyzed individuals stand, to regrowing fingertips, to finding new ways to see inside the body.[123]

In addition to health communication campaigns (addressed in Chapter 2) that focus on disseminating specific health-related findings to improve health, ICs also strive to educate the public about NIH-supported research NIH more generally. For example, the *Biomedical Beat* is a digest of short articles about NIGMS-funded research scientists and images that help illustrate important biomedical concepts and advances.[124] Another project showcases NIBIB bioengineering advances through an interactive online feature, the *Bionic Man* (Figure 10). Users can visually explore some of the latest bioengineering creations from NIBIB-funded research, illustrating recent advancements in tissue engineering, prosthetics, and brain–computer interface technology, among others.[125]

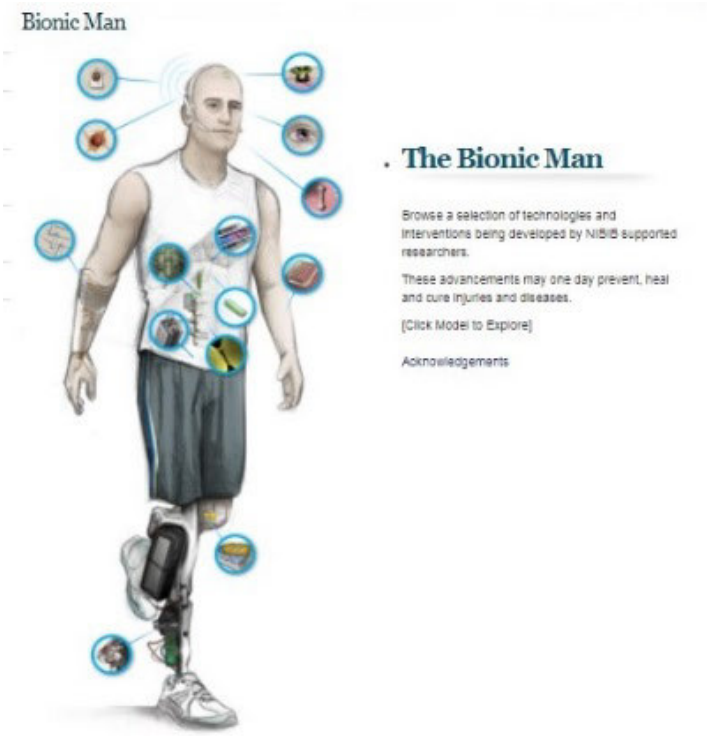

Figure 10. The *Bionic Man* interactive website showcases bioengineering advances. Credit: NIBIB.

[120] https://www.youtube.com/watch?v=I1Bdp2tMFsY&list=PLYH1eUq1QYrqrvA6HRRgKHcPsoJoJA6Kj&index=3.
[121] https://www.youtube.com/watch?v=hTz_rGP4v9Y&list=PLYH1eUq1QYrqrvA6HRRgKHcPsoJoJA6Kj&index=5.
[122] https://www.youtube.com/watch?v=LlPDyl53rZA.
[123] https://www.nibib.nih.gov/news-events/newsroom/nibib-launches-want-be-bioengineer-game-app.
[124] https://biobeat.nigms.nih.gov/.
[125] https://www.nibib.nih.gov/science-education/bionic-man.

Since 1995, OBSSR has sponsored an annual lecture series to provide the public and research community an opportunity to listen to lectures by prominent NIH-funded researchers in the field of behavioral and social sciences. This unique lecture series presents an important overview of the most current topics in scientific literature based on the behavioral and social science research interests across all NIH Institutes.[126]

In February 2014, OBSSR organized a two-day event entitled "Complex Systems, Health Disparities & Population Health: Building Bridges," highlighting the work of the NIH Network on Inequality, Complexity & Health, an NIH-sponsored contract with the University of Michigan. This conference provided information and presentations about the methods and tools of complex systems and how they can be used to address critical determinants of health and health disparities over the life course, including those that involve the health care system, socioeconomic status and mobility, institutions, neighborhoods, behavior, cognitive processes, and neurosciences. The conference brought together different groups from public and health sciences, social sciences, computer and engineering sciences, complex systems, health and social policy, government agencies, and funding agencies who were interested in eliminating health disparities and improving population health.[127]

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 in 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.

[126] https://obssr.od.nih.gov/training/seminars/bssr-lecture-series/.
[127] http://conferences.thehillgroup.com/UMich/complexity-disparities-populationhealth/about.html.

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 are designed to understand basic causes and mechanisms of disease, find new ways of identifying and interrupting disease processes, and bring these new interventions into common practice for public benefit.

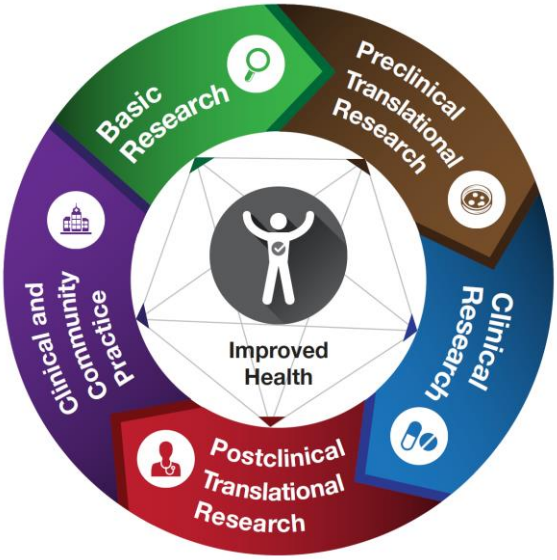

Figure 11. NIH supports the full continuum of biomedical research.

The continuum, from basic research to practice, is summarized below and illustrated in Figure 11. NIH activities relating 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 NIH's 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[128] is research that is conducted with human subjects, and includes patient-oriented research such as clinical trials.[129]

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 postclinical translational research to identify factors that enhance access to and implementation of new

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[128] Clinical research is defined by NIH as:
Research with human subjects that is:

(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 utilize human tissues that cannot be linked to a living individual. It 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

[129] Clinical trials are defined by NIH as:
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.

interventions, with the aim of optimizing the health care delivery system to reflect the latest medical advances.[130] Studies in this area include the development and testing of novel models and methods to best implement newly discovered interventions in order to reach diverse groups and populations (e.g., racial and ethnic groups, rural populations).

Clinical and Community Practice

As an important part of NIH's mission, 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 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.

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 and understanding the basis of health

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

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 between 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 of 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 as well as individual studies using model organisms. Basic research using model

systems and organisms has provided the foundation of knowledge about human growth and development, behavior, the 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.

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 and 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.

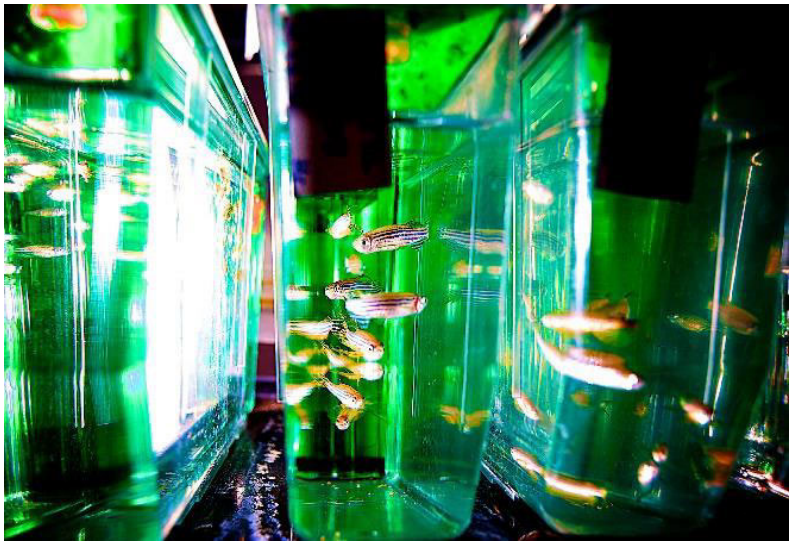

Figure 12. NIH zebrafish facility. Credit: Uri Manor, NICHD.

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, then translate their findings into knowledge to benefit people with those diseases.

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 are poised to take advantage of the wealth of basic research on the cell cycle to develop anticancer drugs that aim to bolster or block cell cycle molecules.

Characterizing Cellular Molecules

-Omics approaches (e.g., genomics, proteomics, metabolomics) characterize cellular molecules, such 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. For many years, the National Human Genome Research Institute (NHGRI) has tracked the costs associated with DNA sequencing performed at NHGRI-funded sequencing centers. It was not that long ago when only one human genome sequence was being generated in the world (by the Human Genome Project). Progress has accelerated quickly—in 2015, the NHGRI Genome Sequencing Program produced enough DNA sequences to equal 14,000 human genomes. Meanwhile, the cost of producing one human genome sequence plummeted from $100 million in 2001 to about $2,000 in 2015 (see Figure 13).[131]

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 to compare the proteome (the entire complement of proteins) of a specific cell type with those

[131] https://www.genome.gov/27541954/dna-sequencing-costs-data/.

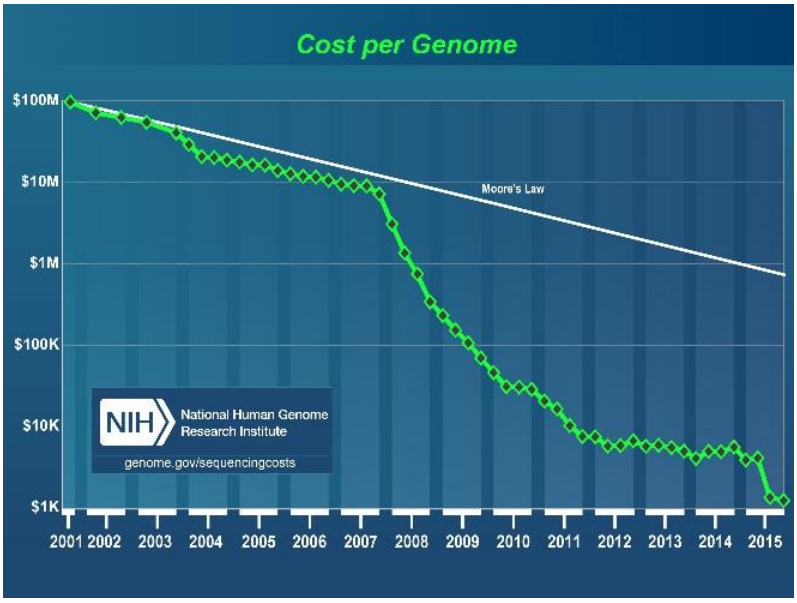

Figure 13. The reduction in cost of sequencing a human-sized genome from 2001 to 2015. Credit: NHGRI.

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.

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.[132]

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. 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

[132] http://www.genome.gov/10000002.

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 cause a person to respond differently to particular pathogens or drugs. Multiple genetic and environmental factors play a role in a myriad of common diseases and disorders. Not all of the genetic risk factors are fully understood, but NIH researchers have begun to identify individual genes or regions of DNA associated with particular conditions.

As a result of the overwhelming influence of the genome on human health, virtually every NIH IC now engages in genome-related research. For example, many ICs fund genome-wide association studies (GWAS)—in effect, full-body DNA scans (using DNA from tissue samples) that are able to identify common variants in common diseases (see Figure 14).[133]

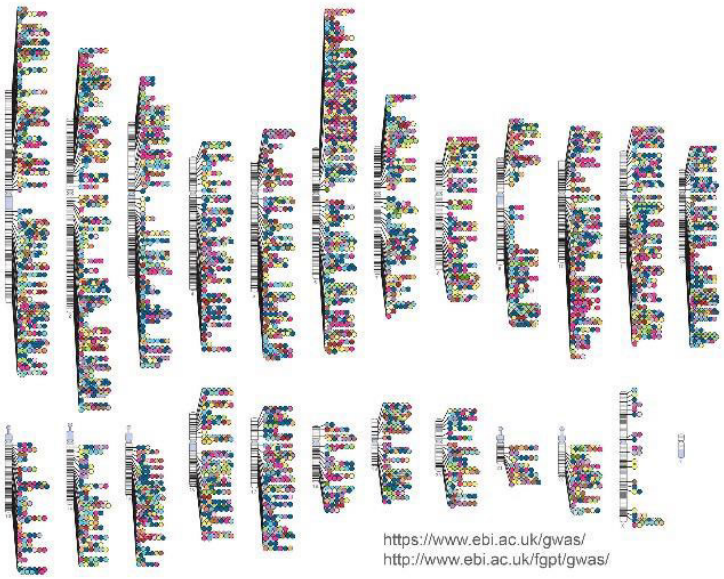

Figure 14. Diagram from the NHGRI Genome-Wide Association Catalog illustrating disease genes that people have found using GWAS. Credit: Darryl Leja and Teri Manolio, NHGRI; Tony Burdett, Dani Welter, and Helen Parkinson, EBI.

Epigenomics

While 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 DNA sequence. Epigenetic processes control normal growth and development and are disrupted in diseases such as cancer. In addition, factors like diet and exposure to environmental chemicals throughout all stages of

[133] http://www.genome.gov/gwastudes.

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 Common Fund's Epigenomics Program is developing resources, tools, and technologies to enable investigations of the role of epigenomic modifications in human health and disease.[134] By 2015, researchers supported by the program mapped the epigenomes of more than 100 types of cells and tissues, providing new insight into which parts of the genome are used to make a particular type of cell. These maps are considered the most comprehensive catalog of epigenomic data from primary human cells and tissues to date.[135]

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 system wide 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 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. The Common Fund's Structural Biology program, supported through FY 2013, was a strategic effort to develop rapid, efficient, and dependable ways to determine the structure of proteins important to human health and disease.[136] Researchers supported through this program developed numerous tools and methods for protein structure determination, characterized the structure of hundreds of proteins, and contributed to the 2012 Nobel Prize in Chemistry for groundbreaking work on a biologically important class of proteins.

Finally, in the growing 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.

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

[134] http://commonfund.nih.gov/epigenomics/index.
[135] Roadmap Epigenomics Consortium, et al. *Nature* 2015;518(7539):317-30. PMID: 25693563.
[136] http://commonfund.nih.gov/structuralbiology/index.

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,[137] 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 of 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 be predictive of 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 Impinge on 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.

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.[138] Health-injuring behaviors such as smoking, drinking, drug abuse, inactivity, and poor

[137] http://www.functionalglycomics.org/static/consortium/consortium.shtml.
[138] Schroeder SA. *N Engl J Med* 2007;357(12):1221–8. PMID: 17881753.

diet contribute to many common diseases and adverse health conditions. Further, 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.[139, 140]

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

[139] Avendano M, et al. *Am J Public Health* 2009;99(3):540-8. PMID: 19150903.
[140] Chapman BP, et al. *Am J Epidemiol* 2010;171(1):83-92. PMID: 19965888.

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 involving rapid synthesis of chemical variants and the high-throughput screening for effectiveness, selectivity, and toxicity. In addition, 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, as consortia make it possible to recruit sufficient numbers of participants to provide the necessary sample for preclinical and clinical study.

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 of the causes of many diseases and the identification of 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 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.[128]

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 or devices, new combinations of drugs, innovative approaches to surgery or radiation 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 employ research approaches assessing 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 the activities of daily life, even as people deal with 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 of insufficient 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 intramural and extramural programs.

Clinical Resources and Programs

The NIH NCATS Clinical and Translational Science Awards (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 needed by local and national research communities 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 AZT); and the development of tests to detect AIDS/HIV and hepatitis viruses in blood, which led to a safer blood supply.

Investigators outside the NIH campus can access the CC's research resources by collaborating with NIH intramural 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.[141]

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[142] database is managed by the NLM.

The *FDA Amendments Act of 2007 (FDAAA)* expanded the scope and purpose of ClinicalTrials.gov. Under *FDAAA*, more types of clinical trials are required to be registered in ClinicalTrials.gov, and additional information about those trials is required 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

[141] https://clinicalcenter.nih.gov/translational-research-resources/index.html.
[142] https://clinicaltrials.gov/.

than 12 months after trial completion date. The law includes penalties for noncompliance. As required by the law, the expanded registration database was launched three months after the law was enacted, results database a year after the law was enacted (September 2008), and the adverse event module the following year (September 2009).

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. It 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 progress of a study from initiation to completion; and (3) obtain summary 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.

In FY 2015, ClinicalTrials.gov added approximately 25,000 registered studies, for a total of more than 200,000 studies, and added summary results information for approximately 3,500 trials, bringing the total to more than 18,000 studies with results data. In addition, an increasing number of studies were posted in ClinicalTrials.gov that identify the genetic variations associated with different outcomes to provide confirming evidence for precision medicine.

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. There are several contributing factors behind this, including the following:

- Many doctors do not suggest clinical research studies to their patients.
- Some individuals may not realize there are a 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 fill out.

- Individuals may face any number of logistical challenges, such as transportation, child care, 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[143] 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[144]—designed to introduce Spanish-speaking citizens 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.

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.[145]

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

[143] https://www.nih.gov/health-information/nih-clinical-research-trials-you.
[144] https://salud.nih.gov/investigacion-clinica/.
[145] http://grants.nih.gov/grants/funding/women_min/women_min.htm.

exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if 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 biennially in aggregate in *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical* Research (see Appendix F).[146] The FY 2013 and 2014 monitoring report indicates that in FY 2014, women constituted 57.2 percent of the participants in NIH-defined clinical research and 36.5 percent of participants were from minority categories. The percentage of female participants has remained fairly stable over the previous 10-year period, ranging from 56.6 to 63.9 percent.

Postclinical Translational Research

Postclinical translational research investigates methods for ensuring that evidence-based interventions are broadly applied and accessible to those who need them 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.[147] Within HHS, AHRQ has primary responsibility for health services research. NIH also supports health services research that focuses 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 utilized 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 most effectively deployed to improve health and well-being, as well as research aimed at designing better interventions with these insights.

[146] https://report.nih.gov/recovery/inclusion_research.aspx.
[147] https://www.drugabuse.gov/sites/default/files/files/HSRReport.pdf.

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. Already a number of NIH Institutes support collaborative activities between health care delivery organizations such as health maintenance organizations (HMOs) 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, and new clinical practices are transmitted and translated for public health and health care service use in specific settings.

Additionally, 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 target 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, such as 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 accessed and understood.

For example, the *NIH MedlinePlus* magazine and its bilingual Spanish counterpart *NIH Medline Plus Salud* are quarterly consumer magazines bringing the latest clinical findings to patients and their families. The magazines complement the *MedlinePlus*[148] and *MedlinePlus en español*[149] websites, provided by NLM, that offer trusted, consumer-oriented health information on more than 975 health topics.

NLM has redesigned many web information services to display effectively for the expanding user base with smartphones, utilizing responsive design to adjust automatically to the size of the user's device. In FY 2014 and 2015, NLM released new responsive design versions of *MedlinePlus, MedlinePlus en español*, and other websites. Use of *MedlinePlus* increased to 409 million unique visitors through the end of 2015; *MedlinePlus en español* had 298.5 million unique visitors, a 37 percent increase. Use of MedlinePlus Mobile increased 37 percent to 1,481,000 unique visitors during the same period. Both sites have a strong social media presence, with nearly 135,000 followers on their Twitter feeds.

An associated resource, MedlinePlus Connect,[150] 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 Connect to provide health information for patients, families, and health care providers using standard clinical vocabularies for diagnoses (problem codes), medications, and lab tests. In FY 2015, MedlinePlus

[148] http://www.nlm.nih.gov/medlineplus/.
[149] http://www.nlm.nih.gov/medlineplus/spanish/medlineplus.html.
[150] https://www.nlm.nih.gov/medlineplus/connect/overview.html.

Connect provided patient education information to 10 million EHR users; there were 67.8 million requests to MedlinePlus Connect.

A monthly newsletter by OCPL, *NIH News In Health*[151] offers the public practical, clear, and to-the-point health news and tips based on the latest NIH research. *Health Information Portal*[152] guides people to relevant, timely health resources from across the NIH website. Both bring the most recent and vetted health information to the public in an accessible, user-friendly format. OCPL also produces *Research Matters*,[153] which highlights research accomplishments by NIH and NIH-funded scientists in a blog-like form 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.[154] The web page 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*. Another site component is translated clinical trials information from the NIH Clinical Research Trials and You website. The new site also features a monthly column called Ask Carla (Pregunta a Carla), designed to provide readers with an opportunity for learning about Spanish-language resources available from NIH.

In addition, information for consumers and clinicians on prevention and treatment of diseases and conditions, as well as reviews of clinical effectiveness research, are available through NLM's PubMed Health database.[155] During FY 2014 and 2015, PubMed Health's collection of systematic reviews expanded from 28,000 to nearly 40,000. PubMed Health's scope was also expanded to include methodological studies for researchers doing systematic reviews.

NLM also provides consumer-friendly information about the effects of genetic variation on human health via NLM Genetics Home Reference,[156] including the basics of human genetics; summaries of more than 1,100 health conditions, diseases and syndromes; and more than 1,300 genes and the health effects of genetic changes. In FY 2015, 152 new summaries were added and 246 existing summaries were updated with new information. Site traffic is strong, with more than 25 million visits from 14.8 million visitors in FY 2015.[157]

NIH continues to broaden its social media presence more generally, utilizing 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[158] 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

[151] https://newsinhealth.nih.gov/home.
[152] https://www.nih.gov/health-information.
[153] https://www.nih.gov/news-events/nih-research-matters.
[154] http://salud.nih.gov/.

[155] http://www.ncbi.nlm.nih.gov/pubmedhealth/.
[156] https://ghr.nlm.nih.gov/.
[157] https://ghr.nlm.nih.gov/.
[158] https://directorsblog.nih.gov/.

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 policy making. 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 policy-making efforts affecting public health. These partnerships include those engaged in improving health and reducing the burdens of disease, such as the many partners across the U.S. government: within HHS (e.g., FDA, CDC, AHRQ) as well as the Veteran's Administration (VA) and the 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 continue to expand their evidence-based public education and awareness campaigns directed at a variety of audiences.

Many campaigns target specific audiences for prevention and treatment efforts. Others focus 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.[159]

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

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 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 showing that tobacco smoking increases 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 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 to 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 risk of cardiovascular disease to factors such as high serum cholesterol levels, hypertension, and cigarette smoking. Based on these results, clinicians were able not only to identify patients at high risk for cardiovascular disease but, even more importantly, 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. NIH efforts to develop and deploy disease registries, databases, and other biomedical information systems to advance biomedical science, health, and health care focus on:

- *Scientific databases.* These databases archive and provide access to authoritative scientific literature, essential research data (including disease-specific data), and clinical research information.
- *Genomic information systems.* These information resources support genetics research and include storage and analysis of genetic data in registries.
- *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.

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 2014 and 2015 to develop or maintain databases, disease registries, and other information resources for the benefit of the larger research community.

In order 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.

- *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 systems (i.e., disease registries and other databases) 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 each other 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,[160] feature the development of significant biomedical information resources,

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

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.

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 development of a particular technology; some projects may take only a few years while others continue for a decade or more.
- Bioengineering research partnerships, which 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 Small Business Innovation Research (SBIR) and Small Business Technology Transfer (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 timeframes.

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 2014 and 2015.

Chapter 3 NIH Research Activities in Fiscal Years 2014 and 2015

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 2014 and 2015 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

Although significant progress has been made in reducing the burden of cancer, cancer is still among the leading causes of death worldwide. In 2012, there were 14 million new cases of cancer and 8.2 million cancer-related deaths worldwide, and the number of new cancer cases is projected to increase to 22 million within the next 20 years.[161] Although U.S. death rates for all cancers combined have decreased since 1995,[162] the increases in diagnoses and cancer survivors will lead to increased national expenditures for cancer care. Therefore, national expenditures are projected to reach $156 billion in 2020 (in 2010 dollars),[163] compared with $143.8 billion in 2016.[164]

Summary of NIH Activities

Cancer research funded and conducted by NIH is critical to the national and global effort to reduce the adverse effects of cancer on the health and lives of patients with cancer, their families, and their communities. Complicating research efforts is the fact that cancer is not a single disease but, rather, includes more than 100 diseases in which genetic changes disrupt cell function.

An example of a key initiative to address diverse research questions related to cancer and needs of patients with cancer is NCI's Provocative Questions (PQ) initiative. The initiative supports research projects that address questions proposed by the scientific community in key areas of cancer research that are deemed important but that have not received sufficient attention or have not been adequately studied. The reissuance of the program in FY 2015 builds on the successes and lessons learned from the

[161] https://www.cancer.gov/about-cancer/understanding/statistics.
[162] https://seer.cancer.gov/report_to_nation/mortality.html.
[163] Mariotto AB, et al. *J Natl Cancer Inst* 2011;103(2):117-28. PMID: 21228314.
[164] https://progressreport.cancer.gov/after/economic_burden.

initiative's first three years to continue to support cancer research in areas that are difficult to address.[165]

Experts from CDC, the North American Association of Central Cancer Registries (NAACCR), the American Cancer Society (ACS), and NCI jointly issued *The Annual Report to the Nation on the Status of Cancer, 1975-2012,* an update on new cases, deaths, and trends for the most common cancers in the U.S.[166] This report provides the best perspective on long-term trends in cancer incidence rates (numbers of new cases of cancer per 100,000 people in the U.S.) and mortality (death) rates for all races combined. Researchers found continued declines in cancer mortality rates for men, women, and children. During this period, the incidence rates of 7 of the 17 most common cancers in men (colorectal, lung and bronchus, prostate, stomach, larynx, bladder, and brain cancers) declined. The incidence rates of 6 of the 18 most common cancers in women (cancers of the colorectum, cervix, lung and bronchus, bladder, ovary, and stomach) decreased. Research also found that, between 2003 and 2012, cancer incidence rates increased among children. An updated *Report to the Nation* covering the years 1975–2014 has been published, with a special section on cancer survival.[167]

In addition to reporting rates and trends for the most common cancers, the 1975–2014 *Report to the Nation* includes a special section on liver cancer. In contrast to overall cancer trends, liver cancer deaths in the U.S. are on the rise and increased at the highest rate of all common cancers in 2003–2012. A major risk factor for liver cancer is hepatitis C virus (HCV) infection. The incidence of new HCV infections was highest in the 1960s through 1980s, before the virus was discovered and preventive measures could be taken. Although the risk of liver cancer for all people increases up to age 85, liver cancer incidence rates were higher among people born during 1945–1965 than among those born in other periods because of higher rates of HCV infection in the 1945–1965 birth cohort.

NCI leads the agency's cancer research efforts; however, many other NIH ICs conduct and support cancer-related research, including the NIH CC, NCATS, NIAID, NIBIB, NICHD, NIDCR, NIEHS, NIMHD, NINR, NLM, Office of Strategic Coordination, and ORWH. NIH supports research on the molecular basis of cancer, prevention and risk factors, screening and diagnosis, treatment, and quality of care as well as the development of cancer research infrastructure and workforce. Total NIH funding for cancer research was $5,392 million in FY 2014 and $5,389 million in FY 2015.[168]

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:

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[165] http://provocativequestions.nci.nih.gov.
[166] Ryerson AB, et al. *Cancer* 2016;122(9):1312-37. PMID: 26959385.
[167] https://seer.cancer.gov/report_to_nation/.
[168] https://report.nih.gov/categorical_spending.aspx.

- Information on FY 2014 and 2015 grants funded
- Assessment of progress in these research fields
- Update on activities in these research fields

Understanding the Molecular Basis of Cancer

One of the most significant challenges facing cancer research today is dissecting the molecular changes that turn normal, healthy cells into cancer cells. One exciting advance for understanding the molecular basis of cancer is development of the Cluster-Chip. A team of bioengineers, molecular biologists, and clinicians used a novel cell sorter to isolate breast cancer cells from patients' blood with the aim of identifying the most effective drugs to treat each patient's tumor.[169,170] The cells, called circulating tumor cells (CTCs), were isolated and grown in the laboratory for extensive genetic analysis, enabling the identification and testing of the most effective cancer-killing drugs for those tumors. The researchers also developed a microfluidic chip (which uses very small amounts of fluid) that can capture rare clusters of CTCs, which could yield important new insights into how cancer spreads. Clusters are even less common than single CTCs, and the unique Cluster-Chip capture technique is based on the structural properties of CTC clusters rather than their size or the presence of surface proteins. Being able to analyze immune cells in CTC clusters would provide a molecular snapshot of tumor-associated immune cells to help us better understand how they contribute to cancer progression and, importantly, how we might be able to alter them to destroy instead of promoting the tumor. In addition to developing new technologies, NIH-supported researchers have used a diverse array of approaches, including genomics, proteomics, cell biology, and epigenetics, to understand how specific molecular mechanisms influence cancer onset, progression, and severity.

Genomics, Proteomics, and Epigenetics

Genes and proteins are often altered or misexpressed in a cancerous state. Researchers supported by NIH conducted numerous analyses to understand how individual genes or proteins regulate the transition from a normal cell to a cancerous cell or to understand why some cancers are less responsive to standard treatments. In addition to identifying changes at the level of a single gene or protein, researchers used approaches to study all of the genes (the genome) and all of the proteins (the proteome) in the human body. Finally, investigators considered how factors upstream of individual genes could influence gene expression, thus leading to a cancerous state.

Understanding how a particular gene or protein works can lead to a greater understanding of factors leading to cancer as well as identification of potential therapeutic targets. In FY 2014 and 2015, NIH-supported researchers uncovered several mechanisms by which individual genes or proteins function.

The NIEHS Mechanisms of Genome Dynamics Group was interested in understanding the factors that lead to the onset of some cancers. They found that a mutation-causing protein, an enzyme known as

[169] Sarioglu AF, et al. *Nat Methods* 2015;12(7):685-91. PMID: 25984697.
[170] Yu M, et al. *Science* 2014;345(6193):216-20. PMID: 25013076.

APOBEC3A (A3A), may be the main cause of mutations in certain cancers, such as those of the bladder, cervix, head and neck, breast, and lung.[171] This finding could have far-reaching implications for the diagnosis and personalized treatment of cancers.

In addition, when NCI scientists studied cells of patients with an extremely rare genetic disease that is characterized by drastic premature aging, they discovered a new cellular mechanism that provides protection from cancer. They found that cells from patients with Hutchinson-Gilford progeria syndrome (HGPS), who typically do not develop cancer, contain a tumor protection mechanism that is mediated by the BRD4 protein.[172] Importantly, they found that this tumor protection mechanism has relevance to more than just patients with HGPS. The same pathway also appears to be at work in the general population, as shown by analyses of clinical outcomes data in several patient groups, including those with breast and lung cancers.

The identification of genetic mutations can lead to a greater understanding of the onset of cancer and provide clues to inform the development of novel treatments and better understand why some cancers do not respond to typical therapies. For example, studies on a protein, DNA-binding inhibitor Id3, have provided insight into cancer immunotherapy (a type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases). Cancer immunotherapy has been recently recognized as a novel and effective therapy for several cancers, including oral cancer.

Certain populations of white blood cells called T helper 9 (Th9) cells play a key role in immunotherapy. NIDCR IRP scientists have investigated the molecular mechanisms by which Th9 cells are generated, and they discovered that Id3 has a critical function in controlling the generation of Th9 cells.[173] This finding could be used to develop new therapies that target Id3 to improve antitumor immunity in cancer.

One of the major reasons for the poor survival rates of individuals with head and neck squamous cell carcinoma (HNSCC) is resistance to chemotherapy. However, the underlying reasons for this resistance are not well known. NIDCR-supported researchers identified a novel molecular mechanism that links increased expression of a protein, TRIP13, to enhanced DNA repair, which in turn leads to the chemotherapy resistance of HNSCC.[174] The study provides initial evidence that targeting proteins involved in DNA repair may reduce tumor cell proliferation (rapid increase in cell numbers) and invasion and therefore prolong the survival of those with HNSCC.

NIH supported numerous studies of the entire genome and proteome to identify genes and proteins that are expressed at incorrect levels in different types and stages of cancer. A major obstacle to targeted cancer therapies (which attack specific types of cancer cells with less harm to normal cells) is our limited understanding of the molecular changes that cause a normal cell to turn into a cancer cell and enable it to survive in a variety of locations in the body. Advances in genomics, bioinformatics (the

[171] Chan K, et al. *Nat Genet* 2015;47(9):1067-72. PMID: 26258849.
[172] Fernandez P, et al. *Cell Rep* 2014;9(1):248-60. PMID: 25284786.
[173] Nakatsukasa H, et al. *Nat Immunol* 2015;16(10):1077-84. PMID: 26322481.
[174] Banerjee R, et al. *Nat Commun* 2014;5:4527. PMID: 25078033.

science of using information technology to organize and analyze large amounts of biological information), and high-throughput screening methods have provided us with tools to identify and understand molecular alterations in cancers. Such discoveries may provide crucial targets for the development of cancer therapies.

To accelerate this research, NIDCR invests in the development of comprehensive datasets that catalog cancer genomes and their representative mutation profiles, epigenomes (alterations that cause changes in gene expression without changing the DNA sequence of that gene), and transcriptomes (the full set of genes expressed in a sample). The Institute has also funded a new cancer genomics initiative to explore the utility of currently available datasets to identify novel targets for oral cancer therapy.[175]

In some instances, knowing the full complement of genes and proteins that are misregulated, meaning that they are expressed at higher or lower levels than in normal cells, may lead to a greater understanding of the cellular processes that go awry in cancer cells. For example, the Barrett's Esophagus Translational Research Network (BETRNet) was developed by NCI with the objectives of achieving a better understanding of esophageal adenocarcinoma (EAC) biology; examining research opportunities associated with its only accepted precursor lesion, Barrett's esophagus (BE); and improving EAC prevention.

Using a genomic approach, BETRNet investigators challenged the accepted paradigm that BE progresses to EAC in a stepwise manner with loss or inactivation of tumor-suppressor genes that are known to prevent a cell from obtaining cancerous properties. Rather, they found that EAC often emerges through a rapid path that involves genome doubling of mutated cells followed by acquisition of oncogenic (tumor-causing) amplifications. This may explain why endoscopic screening of patients with BE frequently fails to detect the patients with the highest risk for cancer.

In a separate study, investigators identified key genetic drivers (including new and known regulators that can cause a cell to become cancerous) that are essential for cell proliferation in highly proliferative luminal breast tumors, for which very few therapeutic options are available.[176]

Tumors are composed of multiple types of cells, including a mixed population of malignant cells, infiltrating immune cells, and stromal (connective tissue) cells. Our knowledge is extremely limited regarding the exact composition of these cells and how they interact dynamically in contributing to tumor growth, metastasis, and drug response. A study related to this area using single-cell RNA sequencing technology uncovered, for the first time, high-resolution gene expression profiles of individual cells from 19 human melanoma tumors, including malignant, immune, stromal, and endothelial cells.[177] This result will help us understand the complexity of the gene expression program of various types of cells in a tumor and will aid in the design of new therapeutic approaches tailored to the needs of an individual in the precision medicine era.

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[175] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-15-004.html.
[176] Gatza ML, et al. *Nat Genet* 2014;46(10):1051-9. PMID: 25151356.
[177] Tirosh I, et al. *Science* 2016;352(6282):189-96. PMID: 27124452.

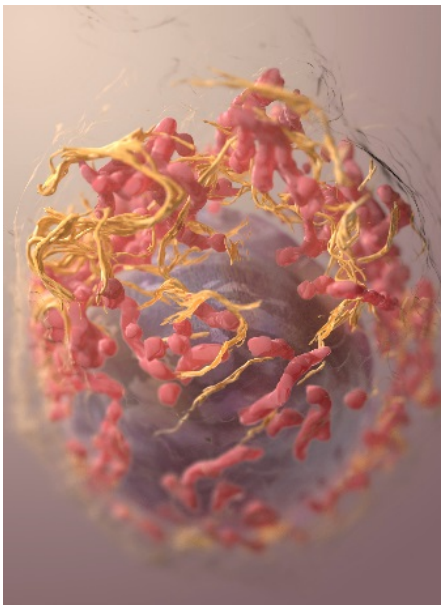

Figure 15. Three-dimensional (3D) structure of a melanoma cell derived by ion abrasion scanning electron microscopy. Credit: Sriram Subramaniam, NCI.

In addition to studies examining genomic modifications in cancer cells, NCI's Clinical Proteomic Tumor Analysis Consortium (CPTAC) applies standardized proteomic workflows/assays to genomically characterized tumors to identify proteins systematically that are derived from alterations in cancer genomes and related biological processes. This approach provides an understanding of the molecular basis of cancer that is either difficult or not possible to obtain through genomics and is critical in the identification/verification of clinical targets. All data and analytical tools are made broadly available to the research community through public databases to maximize their utility and public benefit.

One member of the consortium published a report on the protein signatures of colorectal cancer tumors whose genomes were previously sequenced in a collaborative study by The Cancer Genome Atlas (TCGA) that was supported by NCI and NHGRI and has generated comprehensive, multidimensional maps of the key genomic changes in 33 types of cancer.[178] These investigators found that somatic variants (DNA alterations that arise after conception) displayed reduced protein abundance compared with germline (inherited) variants.[179] Interestingly, the abundance of messenger RNA (mRNA) transcripts, the precursors to proteins, did not reliably predict protein abundance differences between tumors.

Genomic analyses also provide insight into the severity of the disease and identifies candidates for therapeutic targets. NIH-funded researchers led a study designed to identify genetic aberrations associated with metastatic castration-resistant prostate cancer. In this study, researchers conducted whole-exome (regions of DNA that can be transcribed into mature RNA) and RNA sequencing of bone or soft-tissue tumor biopsies from a cohort of 150 men.[180] They identified a number of new genomic alterations enriched in the metastatic tissue compared with primary prostate cancer, including

[178] https://cancergenome.nih.gov/abouttcga/overview.
[179] Zhang B, et al. *Nature* 2014;513(7518):3827. PMID: 25043054.
[180] Robinson D, et al. *Cell* 2015;161(5):1215-28. PMID: 26000489.

aberrations in *BRCA2*, *BRCA1*, and *ATM* genes, in 19 percent of the patients. This study points to several new potential treatment targets in advanced prostate cancer.

Another study focused on the genomic profile of adenoid cystic carcinoma, a particularly aggressive subtype of salivary gland tumor that frequently recurs many years after the initial surgical removal. The identification of genetic changes that are associated with tumor recurrence will not only increase our knowledge about this process, but will also suggest new therapeutic strategies. To discover these genetic changes, NIDCR-supported investigators analyzed genomic signatures of normal and adenoid cystic carcinoma tissues.[181] They detected a unique adenoid cystic carcinoma genomic signature and identified a protein complex that is a potential target for future treatments.

Other factors can influence the levels and timing of gene or protein expression, and these changes in expression can influence the onset and responsiveness of cancers. Epigenetics is the study of modifications of gene expression that do not alter the DNA sequence itself. Epigenetic changes can include the addition or removal of molecules on the DNA or on nucleosomes (protein complexes wrapped by DNA) and can regulate how compact the DNA regions are. For example, one researcher, supported in part by the NIH Common Fund's Epigenomics Program, discovered molecular changes in DNA in skin that had been exposed to sunlight. This finding suggested that epigenetic changes may be an early event that mediates the effects of the environmental damage that leads to skin cancer.[182] Interestingly, the locations of changes in sun-exposed skin overlap with known epigenetic changes in colon cancer, suggesting that these different types of cancers may have underlying molecular similarities.

In addition, NIH-supported genetics researchers have identified a novel long noncoding RNA (RNA that is not translated into a protein), DACOR1, that has the potential to stymie the growth of colorectal tumors.[183] The researchers found that this RNA is present in cells of healthy colons but becomes suppressed in people carrying the disease. More importantly, this RNA interacts with a key enzyme, DNMT1. This protein is responsible for adding methyl molecules to DNA residues in all healthy cells of the body.

In addition to epigenetic changes, the spliceosome may play a role in cancer progression. The spliceosome is a large complex of proteins that removes introns (segments of RNA) through a splicing process to form a mature RNA sequence. An NIH-supported fellow discovered that the spliceosome is a new target of inappropriately activated signaling pathways, or cellular communication signals, in cancers driven by *MYC*, a gene that leads to protumor characteristics when it is overexpressed.[184] The fellow determined that *BUD31*, a key component of the spliceosome, must be expressed for cells to survive overexpression of *MYC*. This research suggests that the spliceosome must be able to function at a high

[181] Gao R, et al. *Oncotarget* 2014;5(24):12528-42. PMID: 25587024.
[182] Vandiver AR, et al. *Genome Biol* 2015;16:80. PMID: 25886480.
[183] Merry CR, et al. *Hum Mol Genet* 2015;24(21):6240-52. PMID: 26307088.
[184] Hsu TY, et al. *Nature* 2015;525(7569):384-8. PMID: 26331541.

level to compensate for increased cancer-causing activity, and components of the spliceosome may be ideal targets for new treatments.

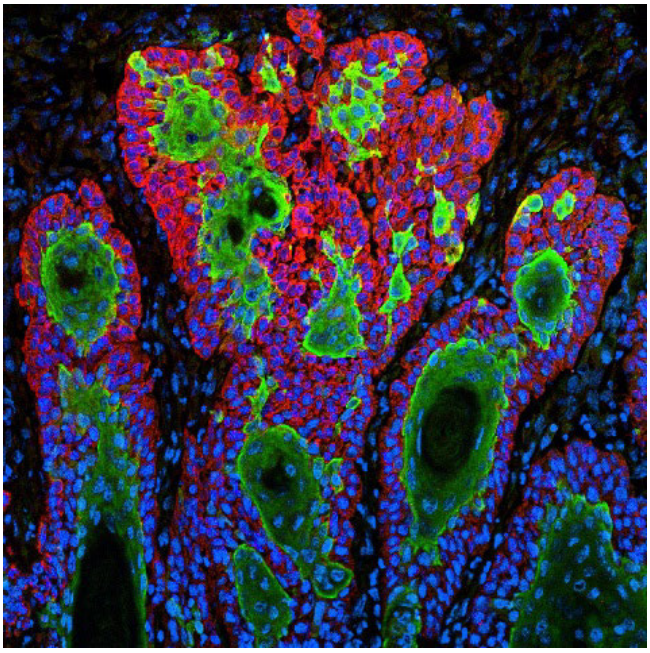

Figure 16. Uncontrolled growth of cells in squamous cell carcinoma, the second most common form of skin cancer. Credit: Markus Schober and Elaine Fuchs, The Rockefeller University.

Signaling Pathways

Cell signaling is a process by which cells can communicate with each other, and this process governs the basic activities of cells and coordinates cellular actions. Cell signaling pathways are often altered in cancerous cell populations, resulting in increased cell division and mobility and decreased cell death dates. Members of the Ras superfamily, a group of proteins involved in cell signaling, are often mutated in cancer cells. Factors that participate in the Ras signaling pathways may be potential targets for anticancer therapies.

For example, a collaborative paper from NIH-funded researchers demonstrated that turning off signaling by KRas, a member of the Ras superfamily, in pancreatic cancer cells results in survivor cells with enhanced function of the mitochondria, the energy-generating cell components. These survival cells are thought to be responsible for tumor relapse. Because these cells depend on mitochondria for energy, blocking this process leads to cell death and could inhibit tumor recurrence.[185] This sequence of events may prove to be a surprising new strategy for combination therapy.

Another study on the link between Ras signaling and pancreatic cancer resulted in the discovery of an enzyme that is associated with disease severity.[186] Using a combination of human tissue biopsies, novel transgenic animal models, and cell culture studies, the researchers established a link between two

[185] Viale A, et al. *Nature* 2014;514(7524):628-32. PMID: 25119024.
[186] Mehner C, et al. *Mol Cancer Res* 2014;12(10):1430-9. PMID: 24850902.

enzymes, MMP3 and Rac1b. Expression levels of Rac1b were significantly associated with the cancer's prognosis. These findings point to inhibition of this pathway as a potential therapeutic strategy for pancreatic cancer.

Researchers also recently identified a new paradigm for metabolic adaption of cancer cells through aberrant Ras signaling.[187,188] They showed that oncogenic Ras stimulates a process known as macropinocytosis, in which cells nonselectively take up large extracellular material (e.g., molecules, nutrients, antigens), and this process has been implicated in tumor metastasis. Cells with mutant Ras proteins use macropinocytosis to internalize proteins from outside the cell and deliver them to the lysosome, where they are degraded to generate free amino acids that can fuel metabolic pathways. This discovery can be used to design new targeting strategies to treat Ras-driven tumors.

The spreading of a tumor along a nerve is considered a marker of poor prognosis and decreased survival rates. Understanding the signaling pathways involved in this process may lead to the identification of useful therapeutic targets to control and prevent tumor invasion. When HNSCC tumors migrate along nerves, the cancer is more likely to spread throughout the body. NIDCR-funded investigators identified a neuropeptide, galanin (GAL), that is involved in the initiation of nerve-tumor crosstalk.[189] The team also showed that GAL is present on nerve cells and activates a signaling protein, GALR2, in the cells. This activation causes the nerves to form new outward projections that help the tumor spread. This study provides important insights into the role of nerves and their growth factors in HNSCC. In another study, NCI investigators showed that a neuronal protein, annexin A2, helps usher another protein, semaphorin 3D (Sema3D), out of pancreatic cancer cells. Once outside the cells, Sema3D joins another molecule to fuel the cancer's spread. Thus, annexin A2 and Sema3D may be new therapeutic targets and prognostic markers of metastatic pancreatic ductal adenocarcinoma.[190]

NIDCR IRP scientists studying cell movement on collagen have identified cell signaling pathways that govern how cells respond to and migrate within a 3D collagen matrix. Collagen is an important protein that is primarily involved in maintaining the structure of many tissues, but it also supports cell movement, including cancer cell migration. Unexpectedly, the dense collagen that characteristically accumulates around advanced tumors and makes them detectable as tumor lumps does not confine cells but, rather, stimulates finger-like cell extensions (invadopodia) that are then used for tumor invasion. Cancer treatment to block the signaling pathways that stimulate the formation of invadopodia may help suppress the spread of human cancers.[191,192]

Finally, recent research suggests that interactions between the microbiome and various cells in the colon may result in the development of colon cancer. Research to define a functional role for specific members of the human microbiome in the development of colon cancer demonstrated that the tumor-

[187] Kamphorst JJ, et al. *Cancer Res* 2015;75(3): 544-53. PMID: 25644265.
[188] Commisso C, et al. *Nature* 2013;497(7451):633-7. PMID: 23665962.
[189] Scanlon CS, et al. *Nat Commun* 2015;6:6884. PMID: 25917569.
[190] Foley K, et al. *Sci Signal* 2015;8(838):ra77. PMID: 26243191.
[191] Kutys ML et al. *Nat Cell Biol* 2014;16(9):909-17. PMID: 25150978.
[192] Artym VV, et al. *J Cell Biol* 2015;208(3):331-50. PMID: 25646088.

promoting activities of the *Fusobacteria nucleatum* bacterium are mediated by several different mechanisms, including (1) expansion of tumor-permissive myeloid-derived suppressor cells (MDSCs), (2) inhibition of tumor-killing natural killer (NK) cells, (3) attachment and invasion of colonic epithelial cells, and (4) formation of complex biofilms that promote the growth of colon tumors.[193,194,195] These insights are important for understanding not only how *F. nucleatum* might promote colon cancer but also how other tumor-associated bacteria might promote cancer.

Furthermore, a study in mice indicated that the gut microbiome may help determine cancer treatment outcomes.[196] NCI scientists found that tumors of germ-free mice (mice completely lacking gut microorganisms) had a largely impaired ability to respond to immunotherapy that slows cancer growth and prolongs survival. The mice also had an impaired ability to respond to mainstay chemotherapy drugs, such as oxaliplatin and cisplatin. These findings in mice may underscore the importance of microorganisms in optimal cancer treatment outcomes in humans.

Metabolism

A central component for cancer growth is the reprogramming of normal cell metabolism to drive uncontrolled growth and the acquisition of new properties that aid cancer cell invasion and metastasis. This reprogramming generates the energy and components that support rapid growth and adapts to the oxidative stress these changes create. While this field began its revival about 10 years ago, the last few years have seen an explosion in our understanding of the extent and variety of the reprogramming that occurs and how it affects the course of cancer progression and response to therapy while also revealing exciting new opportunities for targeting vulnerabilities.[197]

A few relevant studies were conducted to understand how the dysfunction of mitochondria , the energy-generating cell components, may lead to metabolic changes that influence the onset and progression of cancer. The long-held dogma that cancer cells have generally defective mitochondria has given way to a paradigm shift in which these organelles are pivotal in signaling oncogenic growth, differentiation, and progression. Cancer-associated mutations in the nucleus lead to adaptive changes in mitochondrial-dependent tumorigenic signaling and metabolic reprogramming.[198,199] A study provided evidence that genes related to how mitochondria are generated and how they transform energy were differentially expressed during radiation therapy and that these changes were significantly related to changes in fatigue reported by study participants.[200] Changes in biochemical pathways pertinent to the maintenance of mitochondrial integrity, mitochondrial transport mechanisms, and the cell respiratory

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[193] Gur C, et al. *Immunity* 2015;42(2):344-55. PMID: 25680274.
[194] Dejea CM, et al. *Proc Natl Acad Sci USA* 2014;111(51):18321-6. PMID: 25489084.
[195] Wlodarska M, et al. *Cell Host Microbe* 2015;17(5):577-91. PMID: 25974300.
[196] Iida N, et al. *Science* 2013;342(6161):967-70. PMID: 24264989.
[197] https://www.nytimes.com/2016/05/15/magazine/warburg-effect-an-old-idea-revived-starve-cancer-to-death.html?mcubz=0.
[198] Xie Q, et al. *Nat Neurosci* 2015;18(4):501-10. PMID: 25730670
[199] Hirschey MD, et al. *Semin Cancer Biol* 2015;35 Suppl:S129-50. PMID: 26454069.
[200] Hsiao CP, et al. *J Pain Symptom Manage* 2014;48(6):1080-90. PMID: 24786901.

chain (processes through which energy is generated) may partially explain how fatigue develops in patients with cancer who are receiving radiation therapy.

Focusing on Cancer Prevention and Identification of Risk Factors

In addition to working to understand the molecular basis of cancer, NIH aims to reduce cancer incidence by identifying and promoting the modification of behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and developing early medical interventions to interrupt or prevent cancer processes.

A major initiative to address genetic and environmental factors is the Sister Study, which was launched by NIEHS in 2003 and enrolled more than 50,000 women across the U.S. and Puerto Rico. The study participants were women between the ages of 35 and 74 who had a sister with breast cancer. The goal of the study was to increase the likelihood of identifying genetic and environmental risk factors of breast cancer.[201]

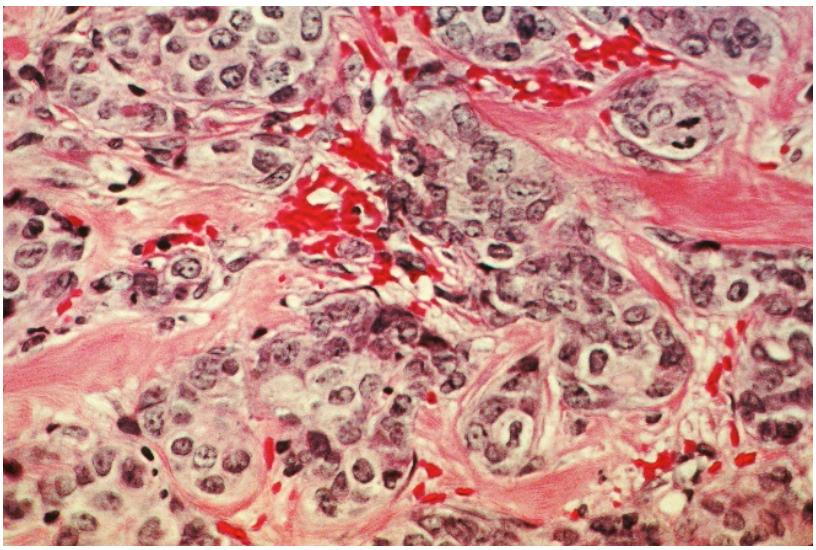

Figure 17. Histological slide of cancerous breast tissue. The pink riverways are normal connective tissue, and the purple cells are cancer cells. Credit: Cecil Fox, NCI.

In 2014, the Sisters Changing Lives Sample Collection was launched, and 4,000 women from the Sister Study were asked to provide a second set of biological and environmental samples to allow expanded basic research on breast cancer.[202] The initiative includes two groups of participants: those who have developed breast cancer since enrolling in the Sister Study and a random sample of other study participants. The second set of samples will help researchers identify changes in biological factors that may be associated with breast cancer development or treatment. The samples from those without breast cancer will allow researchers to evaluate how exposures change over time and help determine

[201] https://sisterstudy.niehs.nih.gov/english/about.htm.
[202] https://sisterstudy.niehs.nih.gov/english/scl.htm.

whether biological changes in patients with breast cancer are due to age and natural variation rather than breast cancer.

NIEHS also supported a study on whether triclosan, an antimicrobial agent commonly found in a broad array of soaps, shampoos, toothpastes and other consumer products, may have adverse consequences for humans. The investigators found that triclosan causes liver fibrosis and cancer in laboratory mice through molecular mechanisms that may be relevant to humans.[203] In an NIEHS-supported study to examine risk factors for acute lymphoblastic leukemia (ALL), findings from the large, pooled analysis reinforced the hypothesis that daycare center attendance in infancy and breastfeeding for at least six months are both associated with a decreased risk of the disease.[204] The earlier the attendance began, the lower the risk was. ALL accounts for 80 percent of childhood acute leukemias, which are the most common cancer in children younger than 15 years.

In addition to research on environmental risk factors, NIH supports research on curtailing behaviors that may lead to cancer. It is well known that tobacco and alcohol contribute to many cancers of the oral region by damaging DNA, but the genes that are damaged are largely unknown. To identify those genetic regions, NIDCR-funded scientists conducted a study to identify mutations that arise in cancers of the upper aerodigestive tract, including those of the oral cavity, larynx, and esophagus. They identified two key genes that may confer a risk for these types of cancers, *RAD52* and *BRCA2*, and the association appears to be stronger in smokers or former smokers than in nonsmokers.[205,206] These two genes are also involved in other cancers, suggesting that targeted therapies for *RAD52* and *BRCA2* may provide new avenues to treat cancers of the upper aerodigestive tract.

NCI leads and collaborates in research and disseminates evidence-based findings to prevent, treat, and control tobacco use. More than four million people per year use the Smokefree.gov resources. NCI also provides the scientific evidence base to inform policy-makers and public health practitioners. Current key focus areas include supporting tobacco regulatory science in collaboration with FDA, supporting research on state- and community-level policy approaches, and informing U.S. Preventive Services Task Force (USPSTF) guidelines on lung cancer screening of smokers and former smokers. In 2014, a series of research papers on electronic nicotine delivery systems were produced by investigators in the State and Community Tobacco Control (SCTC) Research Initiative funded by NCI. The nine articles address marketing of electronic nicotine delivery systems through the internet and social media and at the point of sale, the patterns of and reasons for e-cigarette use, and the impact of price and other tobacco control policies on e-cigarette demand.[207]

Vaccination has been effective in preventing cancer caused by human papillomaviruses (HPVs), a group of more than 150 related viruses, of which more than 40 can be sexually transmitted. Persistent HPV infection by a subset of viral strains is recognized as the cause of virtually all cervical cancers as well as

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[203] Yueh MF, et al. *Proc Natl Acad Sci USA* 2014;111(48):17200-5. PMID: 25404284.
[204] Rudant J, et al. *Am J Epidemiol* 2015;181(8):549-62. PMID: 25731888.
[205] Delahave-Sourdeix M, et al. *PLoS One* 2015;10(3):e0117639. PMID: 25793373.
[206] Delahave-Sourdeix M, et al. *J Natl Cancer Inst* 2015;107(5). PMID: 25838448.
[207] http://tobaccocontrol.bmj.com/content/23/suppl_3.toc.

most anal cancers and a substantial fraction of cancers of the vulva, vagina, penis, and oropharynx. Although two vaccines, Gardasil and Cervarix, are available, considerable work remains. For example, uptake of the vaccines remains relatively low, neither vaccine is effective against all strains of HPV, and long-term analysis of the efficacy of the vaccines is needed.

To help fill these gaps, NCI provided one-year supplement awards to 18 NCI-designated cancer centers to support research aimed at increasing HPV-vaccine uptake by girls and boys aged 11–17 years.[208] In addition, NCI and ORWH are continuing to collaborate in a large, community-based HPV vaccine trial in Costa Rica to evaluate the long-term impact of vaccination against HPV and the immunological mechanisms involved in long-term vaccine efficacy.[209] Ten years of follow-up research are planned to provide a detailed assessment of long-term protection by the vaccine. Finally, the Chinese National Cancer Center (CNCC) joined NCI to lead and cofund a 2014 workshop on cervical cancer prevention and control as part of the Asia Pacific Economic Cooperation. NCI leadership continues to work with CNCC and the Chinese National Cervical Cancer Consortium to provide scientific input on comprehensive cervical cancer prevention in China, including HPV vaccination and cervical cancer screening. These collaborators also continue to advocate for approval of the HPV vaccine by the Chinese regulatory agency and to plan implementation once the HPV vaccine is approved for use in China.[210]

In addition to work supported by NCI, NIAID is conducting two studies on Gardasil. One study is investigating the factors that determine adherence to the recommended vaccination schedule and compares the immunogenicity of Gardasil when it is delivered on the recommended schedule versus when the second and/or third doses are administered substantially later than recommended. The second study in women is determining whether a correlation exists between T- and B-cell responses and antibody levels one to two years after initial vaccination with Gardasil. Investigators also are comparing these immune responses at least three years after the last vaccination in women who received two versus three doses of the vaccine.

NIH supports the development of new HPV vaccines. Building on the success of Gardasil and Cervarix, the NCI's PREVENT Cancer Preclinical Drug Development Program provided funding to support the production and toxicology testing of a second-generation preventive HPV vaccine.[211] Laboratory and preclinical tests have demonstrated that this vaccine has broader effectiveness for a range of high- and low-risk types of HPV than currently available vaccines. The new vaccine is also designed to provide protection from strains of HPV that cause skin warts. In addition, through NIAID's Sexually Transmitted Infections Cooperative Research Centers,[212] investigators are developing a vaccine containing a common antigen that may provide protection from many strains of HPV. The vaccine is in preclinical development.

[208] https://healthcaredelivery.cancer.gov/hpvuptake/.
[209] https://dceg.cancer.gov/research/who-we-study/cohorts/costa-rica-vaccine-trial.
[210] http://www.cicams.ac.cn/Html/News/Articles/1833.html.
[211] https://prevention.cancer.gov/major-programs/prevent-cancer-preclinical/supported-projects.
[212] https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-13-043.html.

NCI has supported studies on the use of biological agents and relevant biomarkers in vaccines for cancer prevention. As an example, vaccines made from peptides may help the body build an effective immune response to kill colon polyp cells. In June 2014, the NCI's Consortia for Early Phase Prevention Trials awarded funding for a randomized Phase II clinical trial of a mucin 1 (MUC1) peptide vaccine to study how well it works in treating patients with newly diagnosed adenomatous colon polyps (growths in the colon that may develop into colorectal cancer over time).[213] MUC1 is abnormally expressed in a variety of cancers, so this vaccine has the potential to prevent the recurrence of adenomatous polyps and the development of colorectal cancer as well as other human cancers.

Finally, NCI supported research on the early prevention of cancer in individuals at high risk. For example, anal cancer rates are rising among people living with HIV. The goal of the Anal Cancer High Grade Squamous Intraepithelial Lesion (HSIL) Outcomes Research (ANCHOR) study is to find the best way to prevent anal cancer among men and women with HIV infection.[214] NCI has initiated a multicenter randomized controlled trial to determine whether treatment of anal dysplasia prevents anal cancer. This trial, which will include 5,000 participants, has the potential to identify a strategy to prevent most cases of anal cancer. Another group supported by NCI investigated the role of aspirin in reducing the risk of colorectal cancer. A multi-institutional team analyzed data and other material from two long-term studies involving nearly 128,000 participants. The researchers found that individuals whose colons have high levels of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) RNA, a gene product, dramatically reduce their chance of developing colorectal cancer by taking aspirin.[215] In contrast, the analgesic provides no benefit to individuals whose colons have low levels of 15-PGDH.

Improving Cancer Screening and Diagnosis

Early detection and treatment of cancer often prolongs long-term survival. Therefore, NIH supports research to identify genetic and epigenetic mutations and biomarkers associated with different types of cancer, fine-tune diagnoses to identify specific cancer subtypes, and develop new diagnostic approaches to detect cancer at its earliest stages. A biomarker is a measurable substance, such as mRNA or protein, in an organism that can indicate the presence of a disease, infection, or environmental exposure. In the case of cancer, biomarkers can be used to diagnose or identify a subtype of cancer.

Many genes are expressed at different levels in the cancerous state compared with the noncancerous state, and identifying these genes may inform future screening and diagnostic efforts. In addition, these changes may provide information about the severity and extent of the disease, thus informing therapeutic decisions.

NCI supported a multitiered genomic analysis of head and neck cancer ties to mutations of the *TP53* gene and losses of the chromosome 3p chromosome.[216] The study determined that high mortality rates

[213] http://prevention.cancer.gov/clinical-trials/clinical-trials-search/nct02134925.
[214] https://anchorstudy.org/.
[215] Fink SP, et al. *Sci Transl Med* 2014;6(233):233re2. PMID: 24760190.
[216] Gross AM, et al. *Nat Genet* 2014;46(9):939-43. PMID: 25086664.

among patients with head and neck cancer occur when *TP53* mutations coincide with 3p deletions. The findings suggest that treatment should be intensified if both markers are present.

In another study, scientists mapped the genetic changes that drive tumors in rhabdomyosarcoma, a pediatric soft-tissue cancer, and found that the disease is characterized by two distinct genotypes.[217] The genetic alterations identified in this malignancy could be useful to develop targeted diagnostic tools and treatments for children with the disease.

A longstanding collaboration between two Specialized Programs of Research Excellence (SPORE) grantees found molecular markers that classify gliomas into molecular groups with distinct clinical features, acquired somatic alterations, and associated germline variants.[218] The molecular markers define five principal groups of gliomas that are associated with histological grade (descriptor that indicates how quickly the tumor is likely to grow and spread), age at diagnosis, and overall survival. This finding will have a transformative effect on brain cancer treatment and provides a simpler molecular genetic means to classify gliomas.

Researchers also identified a genetic mutation in about 20 percent of colorectal and endometrial cancers that had been overlooked in recent large, comprehensive gene searches.[219] With this discovery, the altered gene *RNF43* now ranks as one of the most common mutations in the two cancer types. The *RNF43* mutation may serve as a biomarker that identifies patients with colorectal and endometrial cancer who could benefit from precision cancer drugs that target a particular signaling pathway, although no such drugs are currently available. In animal models, tumors that harbor *RNF43* mutations have been found to be sensitive to new pathway inhibitors that are now in clinical trials in humans.

In a groundbreaking study, NCI researchers published the first report of a germline mutation associated with Hoyeraal-Hreidarsson (HH) syndrome, a clinically severe variant of the inherited bone marrow failure and cancer predisposition syndrome dyskeratosis congenita (DC).[220] Mutations found in TPPI, a member of a protein complex that is significant in human telomere biology, illustrate the importance of this complex in the onset of DC. NCI investigators collaborated with the Center for Rare Jewish Genetic Disorders and the Mount Sinai Genetic Testing Laboratory to evaluate the frequency of another risk variant in *RTEL1*, a founder mutation among Ashkenazi Orthodox and general Ashkenazi Jewish populations. They found the mutation at a high enough frequency to suggest its inclusion in future preconception screening panels for this population. The discovery has improved the lives of patients and families with DC directly, and the gene has been added to genetic screening panels for Ashkenazi Jews.

Researchers assessing gliomas found that mutations in the isocitrate dehydrogenases gene are highly associated with Grades II and III gliomas and associated with better overall survival.[221,222,223] The

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[217] Shern JF, et al. *Cancer Discov* 2014;4(2):216-31. PMID: 24436047.
[218] Eckel-Passow JE, et al. *N Engl J Med* 2015;372(26):2499-508. PMID: 26061753.
[219] Giannakis M, et al. *Nat Genet* 2015;46(12):1264-6. PMID: 25344691.
[220] Kocak H, et al. *Genes Dev* 2014;28(19):2090-102. PMID: 25233904.
[221] Johnson BE, et al. *Science* 2014;343(6167):189-93. PMID: 24336570.
[222] Olar A, et al. *Acta Neuropathol* 2015;129(4):585-96. PMID: 25701198.
[223] Mazor T, et al. *Cancer Cell* 2015;28(3):307-12. PMID: 26373278.

metabolic product of *IDH1* is being explored as a noninvasive biomarker for imaging studies to assess progression or regression of *IDH*-mutant tumors as well as for oncogenic properties related to epigenetics and toxicity in brain cells.

Regions of DNA that reside outside genes can influence the expression levels of nearby genes. NCI researchers identified the first genetic variant associated with a risk of aggressive bladder cancer on chromosome 19 near a gene involved in cell cycle regulation.[224] This result comes from a fine-mapping analysis followed by functional analysis of data from two bladder cancer genome-wide association studies. As the first and the only inherited genetic change identified to date that significantly discriminates between aggressive and nonaggressive bladder cancer, this marker could be useful for inclusion in bladder cancer risk prediction models in combination with established bladder cancer risk factors and other genetic and molecular markers.

Bladder cancer is a heterogeneous disease; some patients have non–life-threatening tumors that grow slowly on the bladder surface, whereas others have malignancies that are classified as aggressive because they grow rapidly, penetrate deeply into the muscle layer, and have high metastatic potential. Increased risk of bladder cancer in carriers of specific heritable genetic variants had already been shown, but no genetic markers had been associated specifically with development of aggressive disease before this study.

Epigenetic modifications may also be used to detect the presence of cancerous cells or determine the severity of the disease. The Extracellular RNA Communication program, supported by the NIH Common Fund and led by NCATS and NCI, is testing and validating extracellular RNA (exRNA; RNA found outside the cell in body fluids, including in fluid surrounding the brain and spinal cord, urine, and blood) molecules to assess their potential to serve as disease biomarkers.[225]

In one Common Fund–supported project, researchers at the University of California, Los Angeles (UCLA), found that saliva contains the same exRNA molecules as in blood and that the molecular profiles of saliva in different people varied in the same way as molecular profiles of blood.[226] The researchers are now exploring how exRNAs in saliva could be used as biomarkers to detect stomach cancer, which is quite deadly because most people do not notice its symptoms until the disease has advanced. This work could enable clinicians to perform simple tests to detect this cancer at earlier stages. In another study, a team of investigators identified a key molecular defect that may have important diagnostic implications in gastrointestinal stromal tumor, or GIST), a tumor that develops in children.[227] They showed that nearly all patients in the study had an epigenetic mutation of a gene that is commonly mutated in GIST.

[224] Fu YP, et al. *Cancer Res* 2014;74(20):5808-18. PMID: 25320178.
[225] https://commonfund.nih.gov/exrna.
[226] https://ncats.nih.gov/pubs/features/searching-saliva.
[227] Killian JK, et al. *Sci Transl Med* 2014;6(268):268ra177. PMID: 25540324.

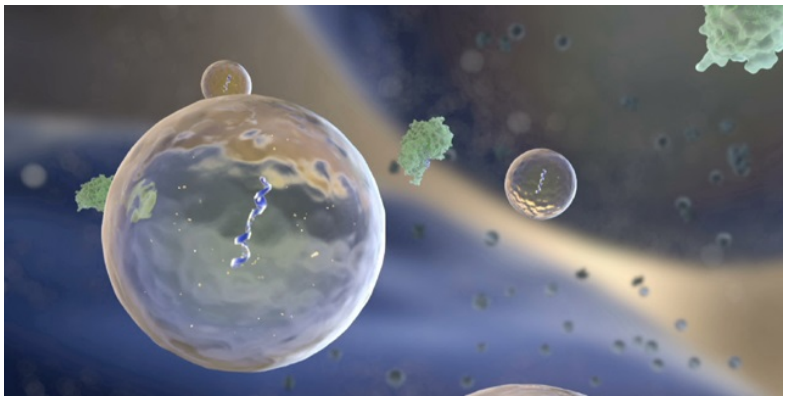

Figure 18. NIH-supported scientists are working to gain a better understanding of a newly discovered type of cell-to-cell communication method based on exRNA. Credit: NCATS.

In addition to genetic and epigenetic biomarkers, researchers are striving to identify other signatures of cancer. To address this goal, NCI launched a three-year initiative in late 2014 to determine whether minimal residual disease (MRD) can be used to predict response to therapy in adult ALL.[228] One team is reviewing the extensive literature demonstrating that MRD can be used as a prognostic and predictive factor in pediatric ALL trials to assess the promise of extending such studies to adult ALL. A second team is working to standardize the measurement of MRD and compare the results gathered with different measurement technologies. The goal of the project is to establish MRD as an indicator of clinical outcomes in adult ALL. It is anticipated that results will be applicable to other diseases, including chronic lymphocytic leukemia, multiple myeloma, and acute myeloid leukemia.

Another study is trying to identify a biomarker for pancreatic cancer by using a factor found in blood. Pancreatic cancer is largely incurable, in part due to the lack of appropriate early detection/screening tools. Recent developments show that exosomes enriched for the proteoglycan glypican-1 are readily detected in the blood of patients with early-stage pancreatic cancer patients; and that the levels of glypican-1–positive exosomes correlate with tumor burden and survival.[229] Exosomes are discrete vesicles the size of viruses found in the blood and urine. They usually carry proteins and nucleic acid cargo and are shed by normal and cancer cells. The unique glypican-1 at the surface of pancreatic cancer-derived exosomes makes them a highly attractive marker to help screen patients for pancreatic cancer at a very early stage with a simple, noninvasive blood test.

Researchers in the NCI IRP analyzed serum from 126 patients with diffuse large B-cell lymphoma (DLBCL) for the presence of circulating tumor DNA (ctDNA) for years after the patients had completed therapy.[230] By measuring the levels of tumor DNA before and after treatment, the team found that the patients who had detectable levels of ctDNA during surveillance were more than 200 times more likely to experience disease progression.

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[228] http://www.fnih.org/what-we-do/current-research-programs/biomarkers-consortium-mrd-project.
[229] Melo SA, et al. *Nature* 2015;523(7559):177-82. PMID: 26106858.
[230] Roschewski M, et al. *Lancet Oncol* 2015;16(5):541-9. PMID: 25842160.

NIDCR-supported researchers also identified a link between ctDNA and cancer. Approximately two-thirds of oral and pharyngeal cancers are diagnosed in later stages. Current diagnostic methods make the detection of early disease and recurrent disease as well as assessment of response to treatment challenging. The investigators showed that ctDNA can be detected in the saliva and plasma of patients with oral and pharyngeal cancer and is a useful marker for early detection and monitoring of therapy outcomes in HNSCC.[231] This new noninvasive method is expected to be cost-effective and to have a similar cost to traditional imaging approaches. In addition, ctDNA detection could result in patient-specific personalized assays, high accuracy in predicting early HNSCC recurrence, and the ability to reduce or even eliminate the need for the current imaging procedures that have an associated radiation exposure risk.

There is significant diversity in the genetic and molecular makeup of cancers, even those of the same type. Understanding the subtype of cancer may lead to more precise treatment for patients. Investigators from NCI's SPORE centers devoted to skin cancer have collaborated in the analysis of melanoma and uveal melanoma as part of TCGA. Data collected from more than 300 patients with melanoma confirmed the presence of the already known mutations in *BRAF* and *NRAS* and revealed the third most frequent recurring mutation to be *RAC-1* in sun-exposed melanoma.[232] The researchers also showed that a key tumor suppressor, neurofibromin 1 (NF-1), is lost in melanomas. Loss of NF-1 leads to increased activation of *RAS*. Thus, melanoma can currently be divided into four categories.

In another study that used whole-genome mRNA expression profiling, researchers discovered three molecular subtypes of muscle-invasive bladder cancer: basal, p53-like, and luminal.[233] These molecular subtypes resemble those of basal and luminal breast cancer. The researchers observed that tumors expressing an active *p53* gene signature were consistently resistant to frontline chemotherapy, indicating that "p53-ness" plays a central role in chemotherapy resistance in bladder cancer. This subtyping promises to guide prognosis and patient stratification and to lead to better identification of patients most likely to benefit from therapy.

Finally, a comprehensive TCGA Research Network analysis of 293 lower-grade gliomas using several genomic platforms identified molecular characteristics of lower grade gliomas that are related to their different clinical features.[234] In particular, one subtype of lower-grade glioma has a similar molecular and clinical background to glioblastoma, suggesting that patients with this molecular profile may benefit from treatment with the standard-of-care protocol for glioblastoma. This analysis has the potential to have a significant impact on how patients with these diseases are treated.

[231] Wang Y, et al. *Sci Transl Med* 2015;7(293):293ra104. PMID: 26109104.
[232] Cancer Genome Atlas Network. *Cell* 2015;161(7):1681-96. PMID: 26091043.
[233] Choi W, et al. *Cancer Cell* 2014;25(2):152-65. PMID: 24525232.
[234] Cancer Genome Atlas Research Network, et al. *N Engl J Med* 2015;372(26):2481-96. PMID: 26061751.

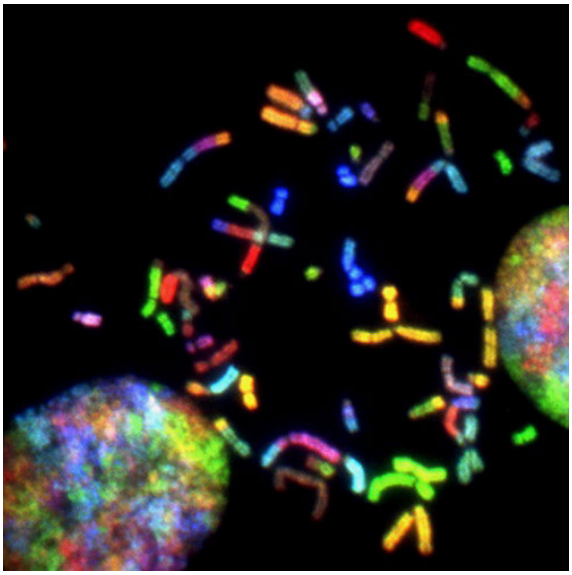

Figure 19. Chromosomes prepared from a malignant glioblastoma visualized by spectral karyotyping reveal an enormous degree of chromosomal instability—a hallmark of cancer. Credit: Thomas Ried, NCI.

In many instances, researchers have used information gained in preclinical studies to develop new diagnostic tests to detect cancer earlier and more precisely. For example, one NCI-supported researcher developed the concept of a synthetic biomarker technology to augment subtle signals from cancer proteins.[235] She then applied this concept to engineer a point-of-care paper test using nanoparticles that can trigger the release of multiple biomarkers in a patient's urine. The test can accurately identify colon tumors and holds promise for improving diagnosis rates for colon cancer in humans. Based on these research findings, the scientist received funding to develop a business plan for a start-up company to commercialize this point-of-care technology and perform clinical trials.

Significant gains have been made in optimizing the screening and diagnosis of cervical cancer. HPVs are a group of more than 200 related viruses, but just two types—HPV 16 and HPV 18—cause about 70 percent of cervical cancers.[236] Therefore, understanding the strain and nature of HPV infection may provide insight into future screening approaches or treatments. For example, if a woman has a positive test result for either HPV 16 or HPV 18, she usually has a follow-up colposcopy test to more closely examine the cervix. To narrow down the diagnosis, NCI investigators developed and evaluated a next-generation sequencing assay that can distinguish women with high-risk HPV 16 cervical precancer from those with HPV 16-positive transient infections.[237] Evaluation of the three-year cumulative risk of cervical precancer among women with positive screening test results for HPV who did not have abnormal cells showed that knowing whether the infection was with HPV 16 (as opposed to another HPV type) was the most important predictor of whether a woman will develop precancerous cells.[238] This finding suggests that HPV 16 genotyping is a useful guide for future testing. Furthermore, the

[235] Warren AD, et al. *Proc Natl Acad Sci USA* 2014;111(10):3671-6. PMID: 24567404.
[236] https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-fact-sheet.
[237] Mirabello L, et al. *Int J Cancer* 2015;136(4):E146-53. PMID: 25081507.
[238] Gage JC, et al. *J Natl Cancer Ins* 2014;106(8). PMID: 25038467.

effective management of HPV infection in women who lack abnormal cervical cells is critical to the introduction of HPV testing into cervical cancer screening.[239,240]

In the largest prospective study to date of image-guided technology for identifying suspicious regions of the prostate to biopsy, researchers compared the ability of this technology to detect high-risk prostate cancer with that of the current standard of unguided prostate biopsy.[241] The image-guided approach, called magnetic resonance/ultrasound (MR/US) fusion biopsy, combines targeted MR imaging with transrectal US to identify regions of suspected cancer to biopsy. The current standard of detection, performed with US alone, uses 12 needles to remove core samples from separate areas of the entire prostate.

Overdiagnosis of cancers is a major public health challenge because it results in overtreatment of non–life-threatening lesions based on screening tests that are becoming increasingly more sensitive and extensively used. The NCI-sponsored Molecular and Cellular Characterization of Screen-Detected Lesions program was funded in late FY 2015.[242] This new initiative, announced in July 2014, awarded grants in September 2015 and builds on the success of pilot data from NCI's Early Detection Research Network (EDRN) on the molecular and cellular differences in screen-detected lesions that are likely to grow slowly, except for a few lesions that progress to become invasive tumors. The initiative created a research consortium to develop molecular and cellular markers of progressive, rapidly growing lesions versus slow-growing lesions detected through screening. The goals of this program are to distinguish cancers that are truly life threatening and require immediate treatment from those for which treatment is unnecessary and to find minimally invasive methods to address the question of how to treat a cancer found through a screening test, thus improving individualized decisions about screen-detected lesions.

In addition, NCI has supported several studies to inform guidelines for cancer screening. In reviewing its breast cancer screening recommendations, the USPSTF considered findings from modeling studies conducted by the NCI-funded Cancer Intervention and Surveillance Modeling Network (CISNET). That key evidence is available, in part, because of the contributions on current screening practices and outcomes from the NCI-led Breast Cancer Surveillance Consortium (BCSC), a well-established research resource for studies designed to assess the delivery and quality of breast cancer screening. This large, standardized dataset presents a unique opportunity for investigators throughout the country to study how mammography screening performance may be improved and how breast cancer screening relates to changes in disease stage at diagnosis, survival, and mortality.

On December 30, 2013, the USPSTF released its updated lung cancer screening recommendation statement based largely on the findings of the NCI-supported National Lung Screening Trial (NLST) as well as modeling studies from CISNET.[243] In addition, NCI supports research exploring the molecular analysis of fecal colonocytes as a noninvasive colorectal cancer screening approach. Other NCI-

[239] Schiffman M, et al. *J Clin Microbiol* 2015;53(1):52-9. PMID: 25339396.
[240] Schiffman M, et al. *Gynecol Oncol* 2015;138(3):573-8. PMID: 26148763.
[241] Siddiqui MM, et al. *JAMA* 2015;313(4):390-7. PMID: 25626035.
[242] https://prevention.cancer.gov/news-and-events/news/consortium-molecular.
[243] https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening.

supported research addresses the development of dual-energy electronic-cleansing computed tomography (CT) colonography, which is also noninvasive, to increase the rate of colon screening by reducing barriers to screening.

Advancing Cancer Treatment

Developing more effective, more efficient, and less toxic cancer treatments is at the heart of the NIH cancer research agenda. NIH-supported research focuses on improving existing cancer treatments, such as chemotherapy and radiation, as well as developing novel, cutting-edge therapies, such as immunotherapy and targeted approaches. New precision medicine efforts will help doctors select the most appropriate treatments based on a genetic understanding of the disease. Special consideration is needed for patients living with HIV and their unique circumstances.

Radiation and Chemotherapy

Radiation, chemotherapy, and frequently a combination of both are often used as the front-line treatment for cancer. Radiation therapy uses high-energy radiation to shrink tumors and kill cancer cells. Chemotherapy is a chemical-based therapy that works by stopping or slowing the growth of cancer cells.

Although both radiation and chemotherapy can kill cancer cells effectively, other healthy cells are often killed in the process, resulting in undesirable side effects. Furthermore, some cancer cells are resistant to both therapies. For example, research supported by NCI showed that non–stem cancer cells can become cancer stem cells in the context of radiation therapy.[244] This issue is particularly problematic because stem cells can give rise to populations of cells that rapidly grow and divide, allowing the cancer to grow and metastasize rapidly. Therefore, considerable effort has been devoted to understanding mechanisms by which these treatments work and developing more specific, more effective, and less harmful types of radiation therapy and chemotherapy.

An NIH-supported researcher demonstrated that ionizing radiation–mediated tumor regression depends on a protein called type I interferon (IFN).[245] He also determined that a particular cell-signaling pathway is required for antitumor effects of radiation mediated by IFN. This is the first report to link this signaling pathway to radiation-mediated immunity, and it provides important insight into the cellular mechanisms of radiation therapy.

In an attempt to improve the accuracy of radiation therapy, investigators have developed and validated an optical surface imaging (OSI) technique to measure lung function and detect breathing irregularities as well as a physical perturbation model for tumor motion prediction.[246,247] A combination of two

[244] Vlashi E, et al. *Int J Radiat Oncol Biol Phys* 2016;94(5):1198-206. PMID: 27026319.
[245] Deng L, et al. *Immunity* 2014;41(5):843-52. PMID: 25517616.
[246] Li G, et al. *Biomed Phys Eng Express* 2015;1(4). PMID: 27110388.
[247] Li G, et al. *Med Phys* 2016;43(3):1348-60. PMID: 26936719.

techniques may become useful in the future to guide radiation beams to a moving target with a reduced treatment uncertainty margin while protecting organs at risk.

The standard radiation therapy for treating cancer is photon radiation therapy, which involves the transfer of pure energy that lacks mass. Proton radiation therapy, in which heavy nuclear elements deliver energy, promises to improve the precision of radiation therapy. In contrast to photon radiotherapy, in which a dose of radiation is delivered all along the X-ray beam as it passes through a patient's body, a proton therapy dose is precisely focused on the target area and little or no dose is delivered to normal tissues in front of or behind the tumor. This feature has made proton therapy particularly attractive to treat tumors in or near the brain or eyes, where the protection of nearby healthy tissues is particularly critical. Proton radiation therapy to treat the most common malignant brain tumor in children is as effective as standard photon (X-ray) radiation therapy while causing fewer long-term side effects, such as hearing loss and cognitive disorders.[248]

In many instances, radiation therapy is used in combination with chemotherapy or other biological treatments. Toward that end, the interdisciplinary NCI-NRG Oncology Sarcoma Working Group formulated a strategic vision for the clinical translation of preclinical findings and the identification of appropriate targeted agents to combine with radiotherapy in the treatment of soft-tissue sarcomas from different sites and/or of different histology subtypes.[249]

Another combination approach, systemic target radionuclide therapy, is a promising treatment that may become more common in future years. One drug, Zevalin, can treat malignant lymphomas by using an antibody with an attached radioactive isotope. The antibody targets the cancer cells while the radiation destroys them.[250] Systemic target radionuclide therapy has been used successfully to treat castration-resistant prostate cancer and bone metastases, suggesting that it is also a promising therapeutic modality for treatment of disseminated solid tumors. Use of this approach with antibodies to interfere with cell-signaling pathways might be a particularly promising strategy.

Although chemotherapy can be effective for treating different types of cancer, patients usually experience severe side effects. One study sought to minimize these side effects by decreasing the chemotherapy dose in patients with Burkitt lymphoma.[251] Standard treatment for Burkitt lymphoma involves high-dose chemotherapy, which has a high rate of toxicity, including death, and cures only 60 percent of adult patients. Adult patients with Burkitt lymphoma had excellent long-term survival rates—90 percent or more—after treatment with low-intensity chemotherapy regimens.

NIH supported numerous clinical trials to test new chemotherapy drugs. For example, patients with advanced treatment-resistant renal cell carcinoma treated with the drug nivolumab demonstrated durable responses that in some responders persisted after they discontinued the drug.[252] Another study

[248] Yock TI, et al. *Lancet Oncol* 2016;17(3):287-98. PMID: 26830377.
[249] Wong P, et al. *J Natl Cancer Inst* 2014;106(11). PMID: 25326640.
[250] Fahey F, et al. *J Nucl Med* 2015;56(7):1119-29. PMID: 25999432.
[251] Dunleavy K, et al. *N Engl J Med* 2013;369(20):1915-25. PMID: 24224624.
[252] McDermott DF, et al. *J Clin Oncol* 2015;33(18):2013-20. PMID: 25800770.

showed that the drug sunitinib maleate was effective in reducing the tumor burden of plexiform neurofibromas (a rare form of benign peripheral nerve tumors) in mouse models.[253]

NIH has also supported research to test combinations of drugs to treat cancer. For example, a study of patients with glioblastoma showed that the addition of the chemotherapy agent bevacizumab to a standard radiation and chemotherapy drug (temozolomide) can prolong progression-free survival (PFS) but not overall survival. [254] Another study showed that the mean survival time of patients with metastatic prostate cancer is longer when androgen deprivation treatment is used in combination with docetaxel, a chemotherapy drug, than with androgen deprivation treatment alone.[255] Finally, a study in patients with a specific type of T-cell Acute Lymphoblastic Leukemia (T-ALL) indicated that a novel combination treatment with the drug nelarabine is highly effective in increasing five-year and overall survival rates.[256]

Researchers also conducted studies to determine which combinations of drugs are most effective for specific kinds of cancer. For example, patients with rhabdomyosarcoma have a poor prognosis at first relapse or disease progression. A randomized trial indicated that the combination of three drugs, vinorelbine, cyclophosphamide, and temsirolimus, was superior to a combination of vinorelbine, cyclophosphamide, and bevacizumab for rhabdomyosarcoma.[257] The combination with temsirolimus will be further investigated in patients with newly diagnosed rhabdomyosarcoma.

Cancerous cells can mutate and adapt to chemotherapy treatments, necessitating an understanding of how some cells "escape" treatments that are generally effective. For example, researchers were interested in understanding how to overcome resistance to the drug bortezomib. [258,259] They found that an enzyme, b-AP15, causes myeloma cells to die and overcomes resistance to the drug. Similarly, another team of researchers demonstrated that an inhibitor of an oncoprotein, a protein that induces a cancerous state, can also reverse resistance to bortezomib. These results pave the way for early-phase clinical trials to test this drug in combination with existing drugs.

Immunotherapy

Immunotherapy is a type of biological therapy that harnesses a patient's immune system to fight cancer. A new method of using immunotherapy to attack tumor cells that have mutations that are unique to a patient's cancer has been developed by scientists at NCI.[260] The researchers demonstrated that the human immune system can mount a response against mutant proteins expressed by cancers that arise in epithelial cells that can line the body's internal and external surfaces (such as the skin). These cells

[253] Ferguson MJ, et al. *Pediatr Blood Cancer* 2016;63(2):206-13. PMID: 26375012.
[254] Gilbert MR, et al. *N Engl J Med* 2014;370(8):699-708. PMID: 24552317.
[255] Sweeney CJ, et al. *N Engl J Med* 2015;373(8):737-46. PMID: 26244877.
[256] https://clinicaltrials.gov/ct2/show/NCT00408005.
[257] https://clinicaltrials.gov/ct2/show/NCT01222715.
[258] Yin L, et al. *Blood* 2014;123(19):2997-3006. PMID: 24632713.
[259] Tian Z, et al. *Blood* 2014;123(5):706-16. PMID: 24319254.
[260] Tran E, et al. *Science* 2015;344(6184):641-5. PMID: 24812403.

give rise to many types of common cancers, such as those that develop in the digestive tract, lung, pancreas, and bladder.

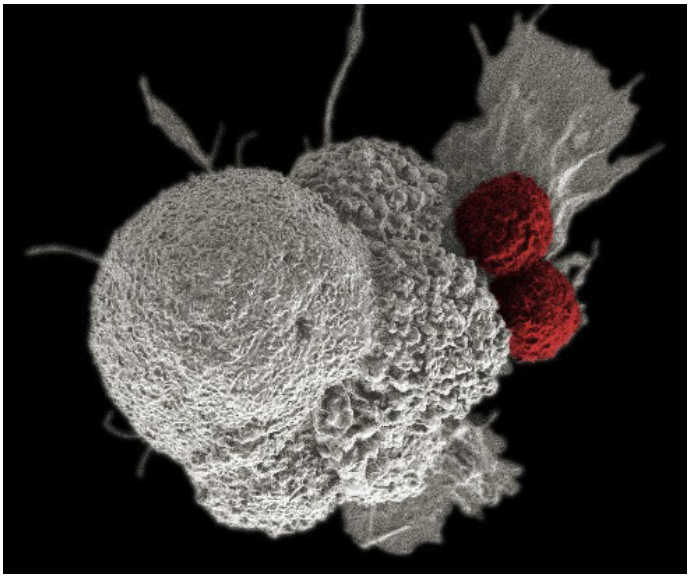

Figure 20. Scanning electron micrograph of an oral squamous cancer cell (white) being attacked by two cytotoxic T cells (red) as part of a natural immune response. Credit: Rita Elena Serda, Duncan Comprehensive Cancer Center at Baylor College of Medicine.

One researcher demonstrated that spherical nucleic acids (SNAs) could train the immune system to fight cancer by modulating a patient's immune response.[261,262] SNAs were designed to deliver glioma-suppressive molecules to silence major drivers of glioblastoma, and this strategy represents a promising new approach for systemic therapy of this deadly brain cancer. Oncolytic viruses that preferentially infect cancer cells have been in development for brain cancer for many years and are now beginning to make some progress in clinical trials.[263,264,265] The viruses have been modified to delete cancer-causing genes and optimize the targeting and destruction of cancer cells. Rare and impressive full recoveries of a few patients have been reported.

Finally, NIH-funded researchers have developed and tested a vaccine that triggers the growth of immune cell nodules in pancreatic tumors, essentially reprogramming these intractable cancers and potentially making them vulnerable to immune-based therapies.[266] The vaccine, GVAX, consists of irradiated tumor cells that have been modified to recruit immune cells to a patient's tumor. The researchers tested GVAX in combination with an immune modulator drug, cyclophosphamide. Cyclophosphamide targets T-regulatory cells (Tregs), a type of immune cell, that typically suppress the immune response of certain T cells that destroy cancer. The reprogramming is designed to make the

[261] Radovic-Moreno AF, et al. *Proc Natl Acad Sci USA* 2015;112(13):3892-7. PMID: 25775582.
[262] Myers BD, et al. *ACS Nano* 2016;10(6):5679-86. PMID: 27192324.
[263] Galanis E, et al. *Cancer Res* 2015;75(1):22-30. PMID: 25398436.
[264] Jiang H, et al. *PLoS One* 2014;9(5):e97407. PMID: 24827739.
[265] Brown MD, et al. *Curr Opin Virol* 2015;13:81-5. PMID: 26083317.
[266] Lutz ER, et al. *Cancer Immunol Res* 2014;2(7):616-31. PMID: 24942756.

tumors more vulnerable to other immune-modulating drugs that have been useful in fighting other cancers.

Genetic Engineering

Adoptive T-cell therapy (ACT) is a form of immunotherapy in which T cells taken from a patient are grown in culture and infused back into the patient to treat cancer. T cells that react to particular tumor antigens may recognize and eliminate tumor cells.

One type of ACT is chimeric antigen receptor (CAR) T-cell therapy, in which T cells are genetically engineered to express proteins that can attack cancerous cells. The CD19 protein, which is found on the surfaces of nearly all B cells (both normal and cancerous), has been shown to be an effective target for this approach.[267] Results from an ongoing clinical trial demonstrated that using T cells engineered to target CD19-CAR T cells in treatment-resistant cases of pediatric and young adult B-cell ALL is associated with strong antileukemia effects and that the treatment is feasible and safe. The success of adoptively transferred tumor-directed T cells requires them to survive and expand in the patient; however, the T cells are often inhibited by cytokines (proteins that carry signals between cells) produced by the tumor. The investigators engineered T cells to express a chimeric cytokine receptor in which one part of the interleukin (IL) 4 receptor was fused to another part of the IL7 receptor.[268] Although tumor-produced IL4 inhibits T cells, the engineered T cells are instead activated by IL4 in preclinical models. In the future, this approach will be adapted for use in patients.

In another study, NK T (NKT) cells were developed as a platform for CAR therapy.[269] NKT-CAR cells were shown to have potent antitumor activity in mouse models and did not induce graft-versus-host disease.

ACT has not been studied extensively in epithelial cancers but has resulted in complete responses in some patients with B-cell malignancies and malignant melanoma. An NCI team designed a clinical trial to study whether cancer-derived T cells that react to HPV, HPV tumor-infiltrating lymphocytes (HPV-TILs), could stimulate tumor regression in women with metastatic cervical cancer.[270] The results of this first clinical trial of ACT to treat metastatic cervical cancer showed that complete regression is possible after one dose of HPV-TILs.

Finally, dendritic cells isolated from patients with Epstein-Barr virus–positive lymphoma were engineered to present Epstein-Barr virus membrane proteins.[271] These antigen-presenting cells were used to stimulate populations of cytotoxic T lymphocytes (CTLs) that were then administered to the patients. Twenty-eight of 29 patients with high-risk disease or multiple relapses who received these cells as adjuvant therapy (in addition to their main treatment) remained in remission at a median of 3.1 years after CTL infusion with little or no toxicity.

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[267] Lee DW, et al. *Lancet* 2015;385(9967):517-28. PMID: 25319501.
[268] Leen AM, et al. *Mol Ther* 2014;22(6):1211-20. PMID: 24732709.
[269] Heczey A, et al. *Blood* 2014;124(18):2824-33. PMID: 25049283.
[270] Stevanovic S, et al. *J Clin Oncol* 2015;33(14):1543-50. PMID: 25823737.
[271] Bollard CM, et al. *J Clin Oncol* 2014;32(8):798-808. PMID: 24344220.

Stem Cell Transplantation

Hematopoietic cell transplantation (HCT), also called hematopoietic stem cell transplantation, can be a curative therapy for patients with severe aplastic anemia (SAA). Although survival after HCT for SAA has improved over the last decade, transplants from unrelated donors generally result in poorer outcomes than those from matched sibling donors. Because sibling donors are not always available, approximately two-thirds of patients have an unrelated donor.

NCI researchers found that among SAA patients younger than 40 years who underwent unrelated donor HCT, longer telomeres in donor white blood cells were associated with longer patient survival after transplantation, regardless of donor age or other transplant-related factors.[272] Incorporating telomere length into other HCT donor selection criteria may allow refinements in donor selection to improve patient survival.

Targeted Therapy

Targeted therapy is a type of cancer treatment that targets the changes in cancer cells that help them grow, divide, and spread. A key advantage to this approach compared with chemotherapy or radiation therapy is that it minimizes off-target effects. Most targeted therapies are either small-molecule drugs that can easily enter cells to target proteins inside the cells or monoclonal antibodies, which are drugs that attach themselves to specific targets on the outsides of cells.

NIH supports research to test existing small molecules and identify new molecules to treat cancer. The mechanistic target of rapamycin (mTOR) signaling pathway is activated in most oral cancers. NIDCR scientists are testing an inhibitor of mTOR, the small molecule metformin that is commonly used to treat type 2 diabetes, for oral cancer prevention.[273] The researchers have shown that metformin treatment reduces tumor cell growth and causes a dramatic reduction in cancer progression in mice. Based on these findings and emerging epidemiological evidence further linking mTOR to oral cancer, a clinical trial was recently launched in individuals with oral lesions to explore the potential use of metformin for oral cancer prevention.

Researchers supported by the NCI National Clinical Trials Network have been conducting Phase II clinical trials focused on recurrent platinum-sensitive ovarian cancer. Results indicate that the combination of the chemotherapy drug cediranib and the targeted drug olaparib results in a significant extension of PFS.[274]

Several preclinical studies have provided insight into potential targeted therapies that use small molecules. The phosphatidylinositol 3-kinase (PI3K) signaling pathway is exploited in nearly every tumor type. However, attempts to use small molecules to target the PI3K pathway to treat cancer have been largely unsuccessful and, in some cases, the drugs increased tumor cell motility and invasion.

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[272] Gadalla SM, et al. *JAMA* 2015;313(6):594-602. PMID: 25668263.
[273] Madera D, et al. *Cancer Prev Res (Phila)* 2015;8(3):197-207. PMID: 25681087.
[274] Liu JF, et al. *Lancet Oncol* 2014;15(11):1207-14. PMID: 25218906.

Researchers studied this oncogenic response to these drugs and determined that cells redistribute active mitochondria in response to these drugs, suggesting that targeting mitochondrial response may be an effective cancer treatment.[275]

In another preclinical study, NCATS and University of Chicago scientists worked together in 2015 to optimize a 3D model of ovarian cancer metastasis.[276] Using the NCATS high-throughput screening facility, this model was screened against 2,420 different small molecule compounds to determine whether any of the compounds had an effect on the metastatic process. Beta-escin, a naturally occurring substance derived from the seeds of the horse chestnut tree, demonstrated an ability to prevent three different metastatic stages and represents a promising lead for further exploration of its therapeutic potential.

Finally, investigators identified a potential target for small molecules resulting in the inhibition of DNA replication. An enzyme, ribonucleotide reductase (RNR), makes the building blocks for DNA duplication, and many anticancer drugs block RNR. However, these drugs can cause adverse side effects because they also block the activity of other enzymes in both cancer cells and healthy cells. NICHD IRP researchers found that IP(3)R binding protein released with inositol 1,4,5-trisphosphate (IRBIT) binds to RNR when the deoxyadenosine triphosphate (dATP) molecule, produced by RNR, is also present, providing a new way to block RNR function.[277] These findings offer new ideas for developing drugs to fight cancer with fewer side effects and less damage to healthy tissue.

A common type of targeted therapy is one that stops angiogenesis, or the formation of new blood vessels. Although antiangiogenic therapy is standard of care for several advanced metastatic cancers, it has failed to prolong overall survival in patients with cancer, especially those whose cancer has spread to the lymph nodes. Researchers developed an experimental model that can be used to test the effectiveness of antiangiogenic therapies.[278] Preclinical and clinical experiments showed that sprouting angiogenesis does not occur during the growth of lymph node metastases and that treatment with two different antiangiogenic therapies using this model showed no effect on the growth or vascular density (number of small blood vessels) of lymph node metastases. These findings provide evidence of a new mechanism of treatment resistance to antiangiogenic therapy and suggest that the class of inhibitors of sprouting angiogenesis will not be effective in treating lymph node metastases.

Precision Medicine

Precision medicine is an approach to patient care that allows doctors to select treatments that are most likely to help patients based on a genetic understanding of their disease. The idea of precision medicine is not new, but recent advances in science and technology have helped speed up the pace of this area of research. PMI, announced in January 2015, includes a focus on cancer (in the PMI-Oncology

[275] Caino MC, et al. *Proc Nat Acad Sci USA* 2015;112(28):8638-43. PMID:26124089.
[276] Kenny HA, et al. *Nat Commun* 2015;6:6220. PMID: 25653139.
[277] Amaoutov A, et al. *Science* 2014;345(6203):1512-15. PMID: 25237103.
[278] Jeong HS, et al. *J Natl Cancer Inst* 2015;107(9). PMID: 26063793.

component). NCI Molecular Analysis for Therapy Choice (NCI-MATCH),[279] part of the PMI-Oncology effort, is a first-of-its-kind Phase II trial in which adult patients with treatment-resistant cancers are assigned to targeted treatments based on the genetic abnormalities in their tumors, regardless of the type of cancer they have. After extensive planning throughout 2014 and 2015, the trial opened for enrollment in August 2015.

The trial uses advanced sequencing and other techniques to characterize patients' tumors at a molecular level. That information is analyzed with a novel and unique informatics system to assign a targeted treatment for that patient. This trial includes more than 20 drugs or drug combinations targeted to known cancer molecular abnormalities. Twenty-five percent of patients are expected to find a matched treatment. The trial is open in the National Clinical Trials Network in a potential 2,400 clinical sites throughout the U.S. The trial is designed to be flexible to give patients access to these drugs quickly and to allow the drugs offered to change in response to new findings. The size and reach of this trial also offers the opportunity to seek treatments for some of the rarer cancer types.

The promise of precision medicine has already been realized in some instances. For example, a clinical trial has shown that patients with a specific molecular subtype of DLBCL are more likely to respond to the drug ibrutinib than patients with another molecular subtype of the disease.[280] Another study demonstrated that patients with non-small cell lung cancer who have a particular genetic marker respond well to the drug crizotinib and have a longer duration of remission than with standard treatments.[281] Finally, investigators have identified genetic markers present in cancer that may increase responsiveness to the drug dasatinib.[282]

Treating Patients with HIV

Patients infected with HIV have a substantially higher risk of some types of cancer than people of the same age who do not have the infection.[283] NCI researchers estimated the total cancer burden in people with HIV infection in the U.S. and how much higher their incidence rate is than that of the population as a whole.[284,285] In 2010, an estimated 7,760 cancers occurred in people with HIV, a rate that is 50 percent higher than in the comparably aged population. The most common excess cancers were non-Hodgkin lymphoma, Kaposi sarcoma (KS), anal cancer, and lung cancer. In another large cohort study, investigators supported by NCI analyzed the cumulative lifetime incidence of cancer in persons with HIV infection who were younger than 75 years and obtained similar results. These studies highlight the large excess burden of cancer in people with HIV infection and will help point the way to targeted public health prevention efforts, such as smoking cessation initiatives.

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[279] http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.
[280] Wilson WH, et al. *Nat Med* 2015;21(8):922-6. PMID: 26193343.
[281] Shaw AT, et al. *N Engl J Med* 2014;371(21):1963-71. PMID: 25264305.
[282] Huang J, et al. *Clin Cancer Res* 2014;20(7):1846-55. PMID: 24486585.
[283] Grulich AE, et al. *Lancet* 2007;370(9581):59-67. PMID: 17617273.
[284] Robbins HA, et al. *J Natl Cancer Inst* 2015;107(4). PMID: 25663691.
[285] Silverberg MJ, et al. *Ann Intern Med* 2015;163(7):507-18. PMID: 26436616.

Sub-Saharan Africa is the center of the HIV epidemic; more than two-thirds of persons with HIV infection live in this region. Interwoven into the HIV epidemic is the rising cancer incidence rate in persons with HIV infection. An initiative funded by NCI and FIC supports highly meritorious, interdisciplinary, multiproject research on HIV-associated malignancies.[286] The projects are being conducted by collaborative consortia made up of institutions in Africa and the U.S. These consortia will enhance the research capacity of African institutions so that they become independent, competitive research centers.

To address issues related to this vulnerable population, NCI launched the Provocative Questions in Cancer with an Underlying HIV Infection initiative. The purpose of this initiative is to advance our understanding of the risks, development, progression, diagnosis, and treatment of malignancies in individuals with an underlying HIV infection through research directed at addressing one of several proposed PQs.[287,288] These PQs are not intended to represent the full range of NCI's priorities in HIV/AIDS-related cancer research. Rather, they are meant to challenge researchers to think about and elucidate specific problems and paradoxes in key areas of AIDS-related cancer research that are deemed important but have not received sufficient attention.

Patients with HIV infection and lymphoma were previously excluded from receiving autologous blood stem cell transplants (using their own blood stem cells after chemotherapy) as treatment due to concerns that these patients' compromised immune systems would give them a higher risk of infection and poor graft function. However, an NIH-supported trial testing the efficacy of blood stem cell transplants in patients with HIV infection found an estimated one-year PFS rate of 82.3 percent in these patients, all of whom had not responded to or had stopped responding to prior therapy.[289,290]As a result, it is now recommended that patients with HIV-associated lymphoma who meet standard eligibility criteria receive an autologous blood stem cell transplant as standard of care.

Improving Quality of Care

Research on the quality of cancer care is essential to ensure the best outcomes for all who may be affected by cancer. Research in this area is addressing improvements in technology during treatment, patient mental health, and posttreatment surveillance and rehabilitation. Key advances related to enhanced quality of care of patients with cancer include the following:

- An NIH-supported collaborative effort led to development of a wireless handheld device that provides real-time objective monitoring of tissue oxygenation during surgery, which helps assess the health of the tissue throughout the procedure.[291] This device is reportedly more reliable than surgeons' subjective procedures that promote tissue healing and significantly reduces both

[286] https://www.cancer.gov/about-nci/organization/oham/hiv-aids-research/oham-research/research-africa.
[287] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-15-012.html.
[288] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-15-013.html.
[289] https://clinicaltrials.gov/ct2/show/NCT01141712.
[290] http://www.hematology.org/Newsroom/Press-Releases/2014/3479.aspx.
[291] Servais EL, et al. *Surg Endosc* 2011;25(5):1383-9. PMID: 20972585.

complication rates and total costs. Originally, this device was created for a study related to surgery to remove all or part of the esophagus. However, the potential additional clinical applications for this device are diverse and include assistance with breast reconstruction and multiple surgical procedures involving the liver and heart.

- Increased anxiety in patients can lead to several negative effects, including decreased treatment adherence, longer hospital stays, and poorer quality of life. Higher levels of anxiety are also associated with other symptoms, including dyspnea (difficult or labored breathing), fatigue, nausea, and pain. Researchers have identified a potential genetic link between anxiety and inflammation. They found genetic variations in cytokines.[292] These variations code for differing levels of cytokines in the body, leading to differing levels of inflammation and of anxiety and other symptoms. Understanding the underlying pathways of anxiety and other symptoms may lead to improved quality of life for patients with cancer and their caregivers.
- The Molecular Epidemiology Resource supported by one of NCI's SPORE programs was used to examine the utility of posttherapy surveillance imaging in a large cohort of patients with DLBCL.[293] The investigators found that most DLBCL relapses are detected outside planned follow-up, and the results showed no difference in outcomes in patients with a DLBCL relapse detected during a scheduled visit compared with patients with relapse detected outside a planned follow-up visit. Therefore, this study does not support the use of routine surveillance imaging for follow-up of patients with DLBCL.
- The Rehabilitation Medicine Department of the NIH CC convened a subject matter expert group to review current literature and practice patterns, identify opportunities and gaps regarding cancer rehabilitation and its support of oncology care, and make recommendations for future efforts that promote high-quality cancer rehabilitation care.[294]

Supporting Cancer Research Infrastructure

Supporting a robust enterprise to advance the science and treatment of cancer is a complex endeavor that requires significant contributions to developing and sustaining infrastructure. NIH contributes to these endeavors by supporting new technologies, biospecimen collection and banking, collaborations and networks, and dissemination and implementation science.

NIH gives high priority to technology development to support research and its application. For this reason, NIH supported the development of technology for diagnosing cancerous lesions, increasing the accessibility of research findings, and harnessing nanotechnology to address major barriers in cancer research.

For example, the NCI Center for Biomedical Informatics and Information Technology worked in close collaboration with the Center for Cancer Genomics and three contractors to design and develop an

[292] Miaskowski C, et al. *Support Care Cancer* 2015;23(4):953-65. PMID: 25249351.
[293] Thompson CA, et al. *J Clin Oncol* 2014;32(31):3506-12. PMID: 25267745.
[294] Stout NL, et al. *Arch Phys Med Rehabil* 2016;97(11):2006-15. PMID: 27237580.

analytics framework for large-scale genomics and related clinical data from projects, such as TCGA.[295] These research and development (R&D) platforms will enable cancer researchers to easily access and analyze TCGA data in a cloud environment and to bring their own data and analytical tools to the platform. The findings from this project will be integrated into the NCI Genomic Data Commons to form the basis of a cancer knowledge system.

In another project, NLM and NCI collaborated to automate diagnoses of cancerous lesions. Multiple-biopsy cervix images collected for an NCI biopsy study were annotated with the NLM-developed Boundary Marking Tool.[296] The study determined that multiple biopsies do improve the sensitivity of high-grade cervical cancer detection. This is a key advance, because a single biopsy may miss 30 to 50 percent of high-grade cervical cancers. To refine the Boundary Marking Tool for this use, NLM used a machine learning approach to classify disease severity in digital histology images of the uterine cervix to automate the classification of epithelium into disease grades (normal vs. precancerous). Computer-assisted classification offloads the burden on expert pathologists, provides a second opinion that may reduce interobserver variability, and facilitates greater throughput of diagnosed images. The performance accuracy of NLM's Boundary Marking Tool was 95 percent for distinguishing between normal and precancerous lesions and 88 percent for determining the exact stage of the disease.

NLM and NCI also collaborated to increase access to pathology reports. NLM and the NCI Surveillance, Epidemiology, and End Results (SEER) program worked to remove information about patients from pathology reports to protect their identities in broad national research use. NLM developed a clinical text deidentification software system, NLM-Scrubber,[297] that is capable of deidentifying many kinds of clinical reports with high accuracy.[298]

In another attempt to increase access and in response to the growing burden of cancer, Global Oncology and the NCI Center for Global Health (CGH) launched a free, interactive Web map, the Global Cancer Project Map (GCPM).[299] Policy makers, researchers, and civil society around the world can search this central repository of international cancer control and research projects. One key advantage of the project is the connection of investigators or collaborators in countries with a low or medium Human Development Index (HDI) score, a measure of a country's level of development that takes into account people and their capabilities (e.g., life expectancy, education level), rather than just economic growth.[300] Many of the projects on the GCPM are related to capacity building and/or training, and many of these projects take place in, or have collaborators from, countries with a low or medium HDI score. This tool allows researchers to identify projects in countries where the prevalence of specific types of cancer is significantly higher than in countries with a high or very high HDI score and provides information on local- and country-level cancer registries.

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[295] https://cbiit.nci.nih.gov/ncip/nci-cancer-genomics-cloud-pilots/nci-cloud-initiative.
[296] Guo P, et al. *IEEE J Biomed Health Inform* 2016;20(6):1595-607. PMID: 26529792.
[297] https://scrubber.nlm.nih.gov.
[298] Kayaalp M, et al. *AMIA Annu Symp Proc* 2014:767-76.PMID: 25954383.
[299] http://gcpm.globalonc.org.
[300] http://hdr.undp.org/en/content/human-development-index-hdi.

In addition, NCI recently launched the Oncology Models Forum (OMF), a cancer community resource program that facilitates optimization of basic research on precision medicine.[301] This research requires the oncology community to have full access to the breadth of available models, deep information about what each animal or other model represents vis-à-vis patients, and collaboration opportunities through the OMF environment. The OMF's site will offer transparent access to knowledge and data on oncology models, comparisons of model data with human data, and organization of the animal modeling research community.

In another technology initiative, the NCI Alliance for Nanotechnology in Cancer issued two FOAs to support efforts focused on addressing major barriers in cancer biology or oncology and on developing nanotechnology-based comprehensive solutions. These efforts will be supported through six Centers for Cancer Nanotechnology Excellence and seven Innovative Research in Cancer Nanotechnology awards.[302,303] To further accelerate commercialization of cancer nanotechnology inventions, the Alliance program staff worked with the Center for Advancing Innovation and Medimmune to build the Nano Startup Challenge in Cancer.[304] Furthermore, in collaboration with NIBIB, NCI issued an image-guided drug delivery program announcement focused on real-time image guidance, monitoring, and validation of drug delivery and response.[305]

A biobank is a repository that stores and manages biological samples (biospecimens) for use in research. NIH supports several biobank efforts as well as efforts to build databases that facilitate access to biobanks. In 2014, NCI launched an online library of standard operating procedures (SOPs) related to biospecimen collection, processing, and storage for the NCI Biospecimen Research Database (BRD).[306] The BRD is a free and publicly accessible database that contains peer-reviewed primary and review articles and now SOPs in the field of human biospecimen science. The rebuilt BRD provides improved user navigation and multiple search functions. The goal of the BRD is to share information and increase collaboration on evidence-based biospecimen practices and, ultimately, to increase research reproducibility. The project has an international scope.

NCI completed a survey on the economics of biobanking and released the Biobank Economics Modeling Tool (BEMT),[307] a publicly available, Web-based financial planning tool for biobanks. Biospecimens and biospecimen resources are integral to the advancement of basic and clinical research, and they play an important role in precision medicine. BEMT is designed to enhance the understanding of the economic considerations involved in initiating, operating, and maintaining a biobank to assist with long-term financial planning and cost recovery.

[301] https://nciphub.org/groups/omf.
[302] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-013.html.
[303] https://grants.nih.gov/grants/guide/pa-files/PAR-14-285.html.
[304] http://www.nscsquared.org/.
[305] https://grants.nih.gov/grants/guide/pa-files/PAR-16-044.html.
[306] https://brd.nci.nih.gov/.
[307] https://biospecimens.cancer.gov/resources/bemt.asp.

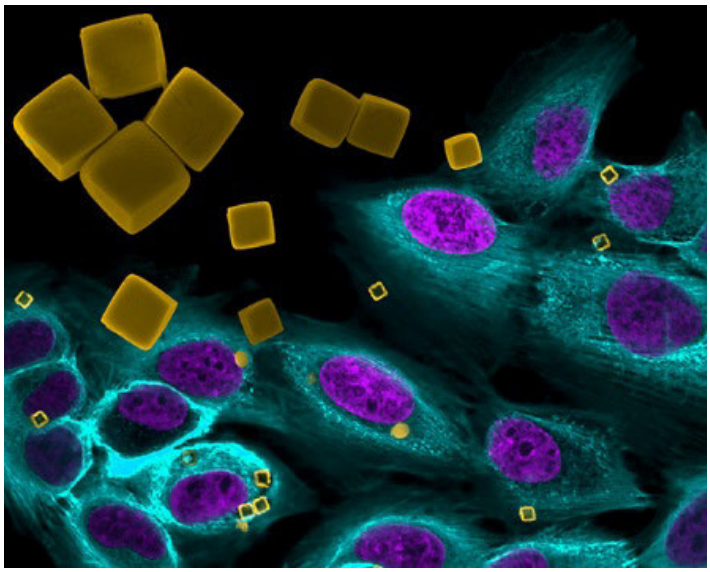

Figure 21. Cancer nanomedicine: The gold cubes are human-made polymer microcarriers, just 2 micrometers wide (in comparison, the diameters of human cells generally range from 7 to 20 micrometers), are designed to transport chemotherapy drugs directly to tumor cells. These experimental cubes, enlarged in the upper left part of the image with a scanning electron microscope for better viewing, have been superimposed onto a second photograph taken with a confocal fluorescence microscope. The image shows similar cube-shaped microcarriers (in yellow) inside cultured breast cancer cells (the nucleus is purple, and the cytoplasm is turquoise). Credit: Jenolyn F. Alexander and Biana Godin, Houston Methodist Research Institute; Veronika Kozlovskaya and Eugenia Kharlampieva, University of Alabama at Birmingham.

The NCI Comprehensive Data Resource (CDR) is a distributed Web-based system that manages and maintains multidimensional data models on biospecimens.[308] CDR was developed and is currently used to gather biospecimens and clinical data on biospecimens collected from patients with cancer and postmortem specimens for NCI's Biospecimen Pre-analytical Variables (BPV) and the NIH Common Fund's Genotype-Tissue Expression (GTEx) programs.[309,310]

Finally, patients who participated in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which started in 2006, were still being followed in 2015 using a streamlined, centralized approach to collect valuable data on cancer in the aging population.[311] The PLCO Biorepository offers high-quality, prediagnostic, serial blood samples that are ideal for investigations of the causes and natural history of various cancers and for pivotal validation of promising, blood-based, early-detection biomarkers.

Biobanks are critical research resources that are dependent on sample donations from patients. In addition, it is essential that biobanks contain specimens from diverse populations. In a special issue of the journal *Cancer Epidemiology, Biomarkers & Prevention*, NCI-funded Community Networks Program Center investigators discussed studies they had designed to better understand why members of underserved populations do not participate in biospecimen donation or clinical trials.[312] The articles

[308] https://github.com/NCIP/CDR.
[309] https://biospecimens.cancer.gov/programs/bpv/.
[310] https://commonfund.nih.gov/gtex.
[311] https://prevention.cancer.gov/major-programs/prostate-lung-colorectal.
[312] http://cebp.aacrjournals.org/content/23/3.

discussed strategies that have successfully engaged such groups in biospecimen collection, prevention, screening, and therapeutic trials. These strategies are essential to advance studies related to cancer health disparities.

NCI released a Spanish-language version of its patient brochure, *How You Can Help Medical Research: Donating Your Blood, Tissue, and Other Samples*.[313] This informative brochure is designed to help patients understand sample donation and the process for donating samples and to improve patient engagement in cancer research.

To ensure that the findings from NIH-supported research are applied outside the laboratory or experimental setting, investments in developing the science to ensure that the lessons learned from research inform and improve the health and health care of the U.S. population are vital. Over the past decade, a consortium of NIH ICs has come together to develop research priorities for this growing field of dissemination and implementation (D&I) research, which builds the knowledge base that informs the optimal integration of scientific discoveries within clinical and community practice. These trans-NIH collaborations have yielded three sets of FOAs,[314] seven large annual conferences on advancing D&I research, and five summer training institutes that have supported more than 200 investigators in their efforts to gain expertise in the field.

NCI recently completed and published a portfolio analysis of NCI's funded grants in D&I research.[315] The analysis, which systematically coded the content of 62 NCI grants in D&I research funded from 2000 to 2012, found that most studies were in tobacco control and colorectal, breast, and cervical cancer screening. There was less focus on understanding uptake of treatments and survivorship interventions. In addition, there has been less emphasis on intervention sustainability, local adaptation of evidence-based practices, intervention scale-up, and de-implementation. The reissuance of the FOAs is intended to address the gaps found in this portfolio analysis.

NIH supports cancer research through increased collaboration. Cancer systems biology addresses dynamic, multifactorial, and complex cancer processes that can only be understood through a combination of experimental and computational approaches. The Integrative Cancer Biology Program (ICBP), which ended in 2015, brought together interdisciplinary teams of experts in biology, medicine, engineering, mathematics, and computer science to address challenging cancer questions and to grow the field of cancer systems biology. During the 10-year ICBP, more than 200 new cancer systems biologists were trained in this interdisciplinary field, and they continue to merge complex cancer datasets with computational modeling to glean important insight into tumor initiation, progression, and treatment. To continue the success in the fledgling cancer systems biology field, NCI is supporting a new initiative, the Cancer Systems Biology Consortium (CSBC), which was launched in 2015 and will support its first research centers and projects in 2016.[316] The CSBC aims to explicitly integrate experimental

[313] https://biospecimens.cancer.gov/content/docs/como-contribuir-a-la-investigacion-medica.pdf.
[314] http://grants.nih.gov/grants/guide/pa-files/PAR-13-055.html.
[315] Neta G, et al. *Implement Sci* 2015;10:4. PMID: 25567702.
[316] https://www.cancer.gov/about-nci/organization/dcb/research-programs/csbc.

cancer biology with mathematical approaches to build predictive models that advance our understanding of cancer biology and oncology.

In addition, the NCI Physical Sciences-Oncology Network (PS-ON) supports innovative ideas that blend perspectives and approaches from the physical sciences, engineering, and cancer research with the goal of improving cancer prevention, detection, diagnosis, prognosis, and therapy.[317] PS-ON investigators develop and test physical sciences–based experimental and theoretical concepts that complement and advance our current understanding of cancer biology and oncology. These investigators have uncovered the complex 3D arrangements of the cancer genome that help us understand the physical processes of oncogene activation and regulation in cancer.[318] By harnessing the principles of evolutionary theory and using novel computational modeling approaches, PS-ON investigators have been able to determine the best doses of chemotherapy to ensure efficacy and minimize toxicity in breast cancer treatment.[319] Based on promising findings in mouse models, related human clinical trials are forthcoming. PS-ON provides training and professional development opportunities for researchers at all career stages with the aim of cultivating a workforce capable of working at the interface of the physical sciences, engineering, and cancer biology.

NIH also supports numerous collaborations among cancer researchers and oncologists, both domestically and globally. The NCI SBIR Development Center hosted its fourth investor forum in Santa Clara, California, in fall of 2014.[320] This event brought together 28 SBIR-funded small businesses and over 100 private investors and strategic partners for a one-day forum to facilitate private investment in technologies for diagnosing and treating cancer. More than 100 one-on-one meetings between investors or strategic partners and SBIR-funded small businesses took place. The investor forum helped facilitate at least six investment or partnership negotiations for the 28 companies in attendance. By 18 months after the event, first-time introductions made at the forum had resulted in an ongoing negotiation for a $4 million investment in a cancer therapeutic company, a partnership to codevelop a much-needed patient-derived xenograft for glioblastoma, and an ongoing financial investment in the development of an imaging device for cancer.

NCI published a program announcement to strengthen cancer prevention and control research programs led by investigators at the NCI-designated cancer centers and institutions in LMICs.[321] Ten awards were made, and one example of meritorious research accomplished through this supplement was conducted by investigators in the U.S., Malawi, and Switzerland. Together, these investigators identified KS virus subtypes and transcripts in patients who had not previously had KS treatment that could be targeted by antiviral drugs and chemotherapy.[322] A second example of meritorious work supported by this funding initiative was accomplished by a collaboration between investigators in the

[317] https://physics.cancer.gov/.
[318] Hnisz D, et al. *Science* 2016;351(6280):1454-8. PMID: 26940867.
[319] Enriquez-Navas PM, et al. *Sci Transl Med* 2016;8(327):327ra24. PMID: 26912903.
[320] https://sbir.cancer.gov/newsevents/events/2014-sbir-investor-forum.
[321] https://grants.nih.gov/grants/guide/pa-files/PAR-15-155.html.
[322] Hosseinipour MC, et al. *MBio5* 2014;5(5):e01633-14. PMID: 25249280.

U.S., the United Kingdom, and four African countries. These investigators characterized the disease burden of esophageal cancer in Eastern Africa so that nations could provide effective oncologic care.[323]

In addition, a formal memorandum of understanding (MoU) was signed by the U.S. and Indian governments to foster cooperation in cancer research, prevention, control, and planning.[324] Signatories included NCI and three key agencies of the Indian government. The MoU aims to strengthen bilateral collaboration in cancer research (including basic, population, clinical, translational, and survivorship research), patient care delivery, infrastructure development, training and capacity building, and assessment and application of new and cost-effective cancer diagnostic technologies for public health.

The NCI CGH held five regional Cancer Control Leadership Forums (CCLFs) in Southeast Asia, Africa, the Pacific, the Caribbean, and Latin America. The goal of the CCLFs is to increase the capacity of participating countries from each region in evidence-based cancer control planning and implementation through a multisectoral approach. Primary focus areas for NCI include (1) supporting the use of available evidence to support planning; (2) promoting strengthened research capacity to improve the ability of countries to use evidence in guiding policy; and (3) providing technical assistance in such areas as cancer registry development, implementation science, prevention, and screening. Evaluation of the CCLF program is currently ongoing to determine its success in achieving its objectives.

Finally, several NCI-designated cancer centers have made significant investments in cancer registries and surveillance in Kenya. A recent NCI evaluation has shown that these global efforts have produced an increase in research capacity building, grant submissions, and collaboration among stakeholders and foreign governments. In response, CGH convened a national stakeholders meeting for more than 40 organizations and 80 individuals across four key technical areas in May 2014. In the years that followed, the National Cancer Institute of Kenya established technical working groups as a direct result of the meeting tracks, and the government of Kenya matched NCI's investment in cancer registries and surveillance. Recently, CGH conducted an evaluation showing that these efforts have resulted in research capacity building, increased grant submissions, and increased collaboration among stakeholders and governments.

Neuroscience

Neuroscience is a multidisciplinary branch of science that brings together biochemical, molecular, developmental, structural, computational, psychosocial, and medical experts to study neurons (nerve cells) and networks of interconnected neurons (neuronal networks). Interestingly, neuronal circuits are made up of a diverse array of neurons and supporting cells, each with unique molecular and functional properties. The role of neuroscience is to provide insights into how the brain and the nervous system

[323] Cheng ML, et al. *Cancer Epidemiol* 2015;39(2):143-9. PMID: 25662402.
[324] http://www.cancer.gov/about-nci/organization/cgh/blog/2015/indiamou.

work to be able to understand our cognitive, social, and physical abilities as well as the mechanisms underlying mental illnesses and aging.

Summary of NIH Activities

Most NIH-funded neuroscience research is central to the missions of several ICs, including NIMH, NINDS, NIDA, NIAAA, NEI, and NIDCD. Many other ICs also fund neuroscience research, notably NIA, NICHD, NCI, NHLBI, NIGMS, NIDDK, NIEHS, and NIBIB, among many others. NIH spent $5.58 billion on neuroscience research in FY 2014 and $5.742 billion in FY 2015.[325] Several neuroscience advances are discussed in the subsections below, and additional examples can be found throughout other sections of Chapter 3.

Understanding the Prevalence, Risk Factors, and Underlying Biology of Neurological Diseases

NIH-funded scientists conduct neuroscience research to understand the biological basis of normal brain function and how these processes go awry in neurological diseases. NIH also supports a variety of research focused on establishing the prevalence of different neurological diseases in addition to identifying various genetic, environmental, and behavioral risk factors that might contribute to their development. At the same time, NIH-funded scientists are working to identify biomarkers to detect the existence, progression, and severity of neurological diseases. Identifying these signals of disease risk and early disease progression will allow the development of earlier interventions to prevent or treat these diseases.

Data from several studies suggest that the rate of dementia, including Alzheimer's disease (AD), is actually decreasing.[326] For example, researchers with the long-running Framingham Heart Study looked at four distinct periods in the late 1970s, late 1980s, 1990s, and 2000s and found that there was a progressive decline in the incidence of dementia at a given age, with an average reduction of 20 percent per decade since the 1970s, when data were first collected. The decline was more pronounced for a subtype of dementia caused by vascular diseases, such as stroke, and was observed only in persons with a high school education and above.

NIH-supported scientists conducting research on the genetic underpinnings of AD are analyzing how genome sequences may contribute to increased disease risk or provide protection from the disease. In FY 2014, NIA awarded grants to support the use of innovative new technologies and computational methods to seek insights into why some people with known risks do not develop the disease. In addition, these investigators will analyze the genome sequencing data generated during the first phase of the Alzheimer's Disease Sequencing Project (ADSP), an innovative collaboration between NIA and NHGRI that began in 2012.[327]

[325] https://report.nih.gov/categorical_spending.aspx.
[326] Satizabal CL, et al. *N Engl J Med* 2016;374(6):523-32. PMID: 26863354.
[327] https://www.nia.nih.gov/news/nih-funds-next-step-cutting-edge-research-alzheimers-disease-genome.

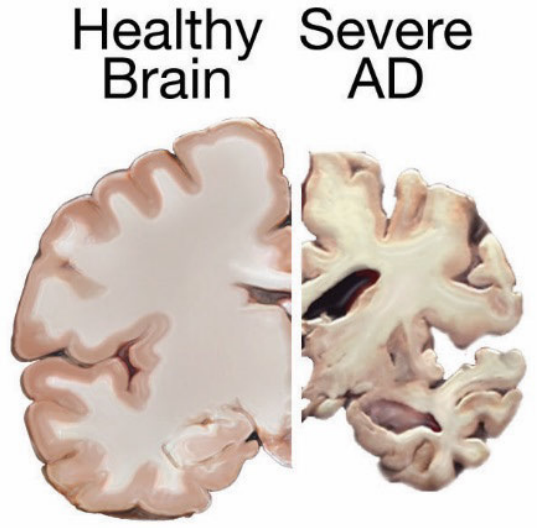

Figure 22. Comparison of a healthy brain and a brain with severe AD. Credit: NIA.

The NIA-funded Pathway Discovery, Validation, and Compound Identification for Alzheimer's Disease study is focused on discovery, characterization, and validation of complex molecular networks and candidate genes that influence susceptibility to cognitive decline and AD. Using cutting-edge computational methods, this multidisciplinary team is analyzing rich clinical, pathological, genomic, and other large-scale molecular data collected from over 1,000 volunteers.[328]

NIEHS published two FOAs in July 2013 that requested applications for NIH support of research linking environmental exposure to AD and other neurodegenerative diseases to expand research in the field of neurodegenerative disease.[329,330] The research proposals solicited ranged from basic mechanistic exposure studies to human-based studies as well as adaptations of new technologies, tools, and methods for use in studies of neurodegenerative diseases. Of the many applications received for both FOAs, at least 12 meritorious projects were funded.

Scientists have identified a possible cellular mechanism triggered by oxidative stress and DNA damage that is linked to tau, a protein commonly found in the brains of people with AD, and certain other neurodegenerative diseases called tauopathies. The effect was observed in fruit fly and mouse tauopathy models and in the brains of human patients with AD. The research suggested a novel pathway in tauopathies by which oxidative stress may lead to a change in chromatin—a complex of DNA and proteins that is found in the nucleus of a cell—that is not seen in the normal aging brain.[331] Analysis indicated that this change in chromatin leads to abnormal gene expression and identified chromatin structure as a potential therapeutic target for AD.

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[328] https://projectreporter.nih.gov/project_info_description.cfm?aid=8921931&icde=36556499.
[329] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-13-006.html.
[330] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-13-007.html.
[331] Frost B, et al. *Nat Neurosci* 2014;17(3):357-66. PMID: 24464041.

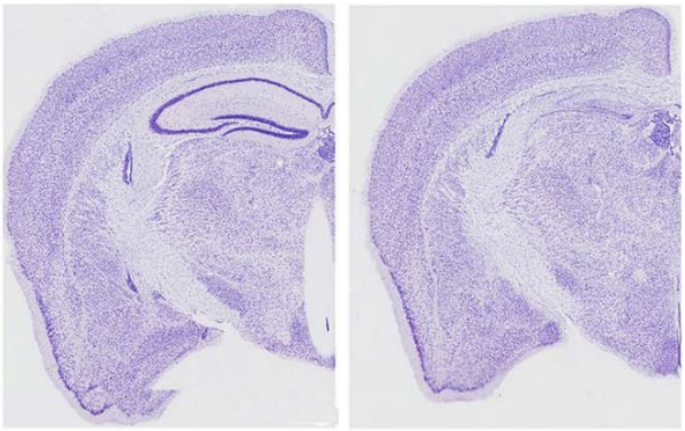

Figure 23. Sections of brains from normal mice (left) and mice with tauopathy-induced neuronal degeneration (right). The dark purple lines in the image on the left outline the hippocampus, the area most responsible for learning and memory. This structure is almost completely absent in the right image. Credit: Ashe Lab, University of Minnesota.

NIA-supported researchers recently developed an innovative method to culture human brain cells in the laboratory and then modeled, for the first time, the cascade of cellular changes involved in the onset and progression of AD.[332] The findings support the amyloid hypothesis, a 30-year-old theory that the build-up of beta-amyloid protein in the brain kick-starts the toxic changes that lead to tau tangles (primary marker of AD) and, ultimately, cell death.

In addition, the NIA-funded System Approach to Targeting Innate Immunity in AD study is using a systems biology approach to integrate genomic, gene expression, and pathological data from patients with AD and AD mouse models and analyze them in novel ways. The study's goal is to identify and characterize therapeutic targets in the innate immune system.[333]

AD-like symptoms affect as many as half of individuals with Down syndrome (DS) who survive to age 50.[334] Patients with DS have three copies of chromosome 21, which includes the *Bach1* gene. *Bach1* codes for a protein that blocks other genes that help protect cells from DNA damage. Using brain tissue that had been donated by deceased individuals through tissue banks, NICHD-supported scientists compared the amount of Bach1 proteins in four groups of people: (1) young adults who had DS but no AD, (2) older adults who had both DS and AD, (3) young adults with neither condition, and (4) older adults with neither condition. The researchers found that both younger and older individuals with DS had higher amounts of Bach1 proteins than individuals with neither condition, a finding that helps explain why individuals with DS are at high risk of AD at an earlier age than individuals without DS.[335]

NIA-supported investigators have found that older adults who take anticholinergic drugs—which are commonly prescribed for a wide range of health conditions, including overactive bladder, seasonal allergies, and depression—may be at significantly higher risk of developing dementia. The greater the use of the drugs, the higher the risk of dementia. These medications block the neurotransmitter

[332] Choi SH, et al. *Nature* 2014;515(7526):274-8. PMID: 25307057.
[333] https://projectreporter.nih.gov/project_info_description.cfm?aid=8605311&icde=36498692.
[334] Leverenz JB, et al. *Exp Neurol* 1998;150(2):296-304. PMID: 9527899.
[335] Di Domenico F, et al. *J Alzheimers Dis* 2015;44(4):1107-20. PMID: 25391381.

acetylcholine and may cause side effects, such as impaired cognition, especially in older people. This side effect was thought to be reversible once the person stopped taking the medication; however, the new findings suggest that physicians treating older people should prescribe alternatives to anticholinergic drugs, when possible, or lower doses of the drugs.[336] More studies are needed to determine the extent to which stopping anticholinergic drugs can reduce the risk of developing permanent dementia.

Mechanisms underlying the higher incidence of migraine in women are poorly understood. Therefore, in FY 2015, NINDS supported an administrative supplement to explore sex differences in the cellular signaling pathways used to process migraine pain.[337] The researchers are also seeking to identify new therapeutic agents to treat migraine and determine whether there are sex differences in treatment efficacy.

A protein previously linked to acute symptoms after a traumatic brain injury (TBI) may also be responsible for long-term complications that can result from TBI. Using an ultrasensitive technology, researchers were able to measure levels of tau—a protein also known to have a role in the development of AD and Parkinson's disease (PD)—in the blood of military personnel months and years after they had experienced TBI. The researchers found that these elevated levels of tau are associated with chronic neurological symptoms, including postconcussive disorder, which means that the person has such symptoms as headache and dizziness in the weeks and months after the injury.[338] These chronic neurological symptoms have been linked to chronic traumatic encephalopathy—progressive brain degeneration that leads to dementia after repetitive TBIs—independently of other factors, such as depression and posttraumatic stress disorder (PTSD). Moreover, IRP scientists and their collaborators have identified brain imaging markers of PTSD in patients with TBI.[339]

NIDCD-supported researchers used a type of magnetic resonance imaging (MRI), functional MRI (fMRI), on multiple parts of the brain to measure individuals' responses to speech compared with other natural environmental sounds.[340] They found that one area, the superior temporal sulcus, responded solely to speech. A greater understanding of the locations in the human brain where speech is analyzed will help us develop new ideas about how to identify, prevent, and possibly treat acquired and developmental hearing, speech, and language disorders, including dyslexia, auditory processing disorder, and specific language impairment.

Using a sensitive new technology, single-cell RNA-sequencing, NIDCD IRP scientists have created the first high-resolution gene expression map of single cells within the newborn mouse's inner ear.[341] By analyzing the cells' gene activity profiles, the scientists were able to identify genes that are active at different stages of development. The findings provide new insights into how epithelial cells in the inner

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[336] Gray SL, et al. *JAMA Intern Med* 2015;175(3):401-7. PMID: 25621434.
[337] https://projectreporter.nih.gov/project_info_details.cfm?aid=8992200&icde=36489039.
[338] Olivera A, et al. *JAMA Neurol* 2015;72(10):1109-16. PMID: 26237304.
[339] Lopez KC, et al. *J Neurotrauma* 2017;34(1):16-22. PMID: 26942337.
[340] Overath T, et al. *Nat Neurosci* 2015;18(6):903-11. PMID: 25984889.
[341] Burns JC, et al. *Nat Commun* 2015;6:8557. PMID: 26469390.

ear develop and differentiate into the specialized cells that serve critical functions for hearing and maintaining balance. Understanding how these important cells are formed may provide a foundation for the development of cell-based therapies for treating hearing loss and balance disorders.

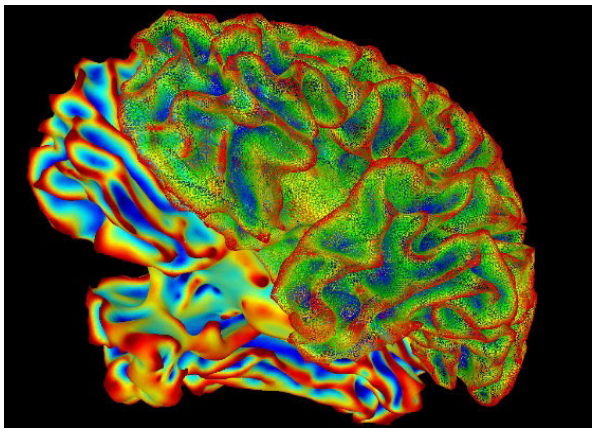

Figure 24. Multicolored image of a whole brain for brain imaging research. This image was created using a computer image-processing program SUrface MApping (SUMA), which is used to make sense of data generated by fMRI. Credit: NIMH.

People who have a poor ability to taste or smell can miss important cues to help them avoid dangers, such as gas leaks, fire, and spoiled food. Scientists in the NIDCD Epidemiology and Statistics Program collaborated with the National Health and Nutrition Examination Survey (NHANES) Division of CDC's National Center for Health Statistics to conduct the first nationally representative survey on perceived taste and smell problems in more than 3,600 adults aged 40 and older.

About 19 percent of U.S. adults aged 40 and older report having had a problem with their ability to taste, and approximately 23 percent report having had a problem with their ability to smell.[342] The likelihood that a person will report a diminished sense of taste and/or smell increases with age. Nearly 31 percent of adults aged 80 years or older report having had a problem with their sense of smell, and more than 27 percent have had a problem with their sense of taste. This survey was part of the Healthy People 2020 national objectives for improving the health of all Americans. The data help us gauge the scope of the problem. Future data releases will also include results of taste and smell tests and will give us our first look at the prevalence of taste and smell problems in the U.S.

NIDCR IRP scientists are exploring how sensory signals are detected by receptors on the tongue and palate and how that taste information is transmitted to the brain. A recent breakthrough was the finding that the signals detected by the receptor cells in taste buds on the tongue are not significantly processed before they reach the brain.[343] These findings solved a long-standing controversy in the field and demonstrated the mode of transmission of taste information from the oral cavity to the central nervous system.

[342] Rawal S, et al. *Chem Senses* 2016;41(1):69-76. PMID: 26487703.
[343] Barretto RP, et al. *Nature* 2015;517(7534):373-6. PMID: 25383521.

In LMICs, where brain disorders have had and are predicted to continue to have a significant impact, research on the causes, prevention, and treatment of neurological conditions and disorders is needed along with implementation research. The FIC Global Brain and Nervous System Disorders Research across the Lifespan program is supporting implementation science research on how to best deliver currently available, low-cost treatments for neurological conditions. The program supports cutting-edge basic research in LMICs on nervous system development, function, and impairment throughout life—research that could lead to new diagnostic, prevention, and treatment strategies that could also provide direct benefits for Americans. For example, an FIC grantee pioneered the choroid plexus ablation technique to treat hydrocephaly (abnormal buildup of fluid in the brain) in Africa, where ventricular brain shunting was not available. This innovative approach is now also being implemented to treat hydrocephaly in the U.S.[344]

Building Models to Understand Neurological Diseases

Given the complexity of the nervous system, it can be difficult to fully characterize the underlying mechanisms that go awry in neurological diseases. In addition, testing in humans can be difficult to do safely, especially given the importance of the brain to so many essential functions and behaviors. Therefore, NIH supports a robust portfolio of disease models and uses model organisms to gain new insights into both how neurological diseases occur and potential interventions.

Some researchers have theorized that, over time, damage from free radicals might contribute to the neurological deterioration in AD and other cognitive decline disorders. To explore this idea, NICHD researchers studied zebrafish, a type of fish that has many genes in common with human beings.[345] The scientists fed zebrafish a diet that lacked vitamin E for 9 months, then examined their brains for changes in brain lipids—key molecules in neuron membranes. When compared with zebrafish fed a diet with sufficient amounts of vitamin E, the vitamin E–deficient fish had major differences in lipids containing a nutrient, docosahexaenoic acid (DHA), that is important for brain development and function. These results help explain why vitamin E is needed for brain health.

Researchers are also making promising advances in understanding and targeting the vascular component of the brain to prevent or treat AD. In FY 2015, researchers supported by NINDS and NIA found that people with AD had lower levels of the phosphatidylinositol binding clathrin assembly (PICALM) protein, which helps remove beta-amyloid from their brain's blood vessels. Increasing levels of the protective form of PICALM on brain blood vessels in mice enhanced beta-amyloid clearance, reinforcing the idea that blood vessels play an important role in clearing toxic waste from the brain.[346]

In other AD research, NIBIB-supported researchers used repeated MRI-guided focused US treatments to reduce the effects of AD in a mouse model, using microbubbles to open the blood-brain barrier and

[344] https://www.fic.nih.gov/About/Staff/Policy-Planning-Evaluation/Pages/fogarty-program-evaluation-brain-disorders.aspx.
[345] Choi J, et al. *J Lipid Res* 2015;56(6):1182-90. PMID: 25855633.
[346] Zhao Z, et al. *Nat Neurosci* 2015;18(7):978-87. PMID: 26005850.

treat the hippocampi of the mice.[347] The treatment led to improvements in cognition and spatial learning that might have been caused by plaque reductions and neuronal plasticity increases resulting from the focused US treatment. They found no tissue damage or negative behavioral changes.

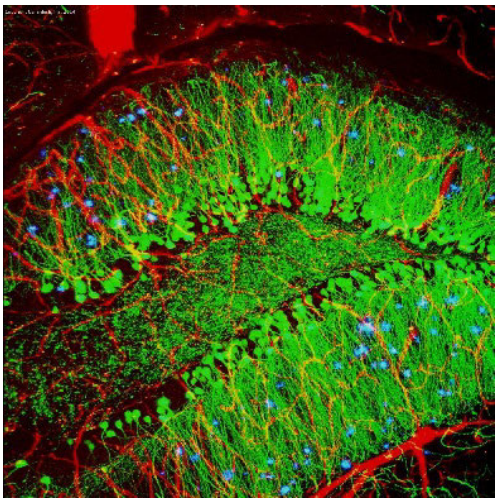

Figure 25. Mouse brain showing plaques (in blue), a hallmark of AD. Credit: Alvin Gogineni, Genentech.

The infantile type of Batten disease, infant neuronal ceroid lipofuscinosis (INCL), is caused by changes in the *CLN1* gene and affects one in 100,000 births. Apparently normal at birth, children with INCL lose their sight by age two years. Around age four years, these children show no brain activity and enter a vegetative state, in which they remain until they die a few years later. No treatment is available. Recently, NICHD researchers used advanced molecular techniques to create a genetic mouse model of INCL.[348] This model will help researchers learn more about the mechanisms underlying this devastating disease and develop effective therapeutic strategies.

Recently, NIDCD intramural scientists used gene therapy in mice to correct one form of inherited deafness. Inheritance of a mutant gene that codes for the whirlin protein causes defects in the architecture and organization of sensory cells in the inner ear (hair cells) that detect sound. Mice with the mutation have severe hearing loss and balance problems, and their hair cells die after birth. In humans, the mutation may cause either deafness alone or Usher syndrome (both deafness and blindness). When scientists treated the mutant mice, the therapy restored the architecture, organization, and survival of the hair cells in the treated ear.[349] The therapy did not, however, restore hearing in the mutant mice. These results are the first to demonstrate that gene therapy can rescue architectural defects in inherited deafness. Now, scientists are eager to figure out why these improvements in the hair cells do not restore hearing ability.

[347] Burgess A, et al. *Radiology* 2014;273(3):736-45. PMID: 25222068.
[348] Bouchelion A, et al. *Ann Clin Transl Neurol* 2014;1(12):1006-23. PMID: 25574475.
[349] Chien WW, et al. *Mol Ther* 2016;24(1):17-25. PMID: 26307667.

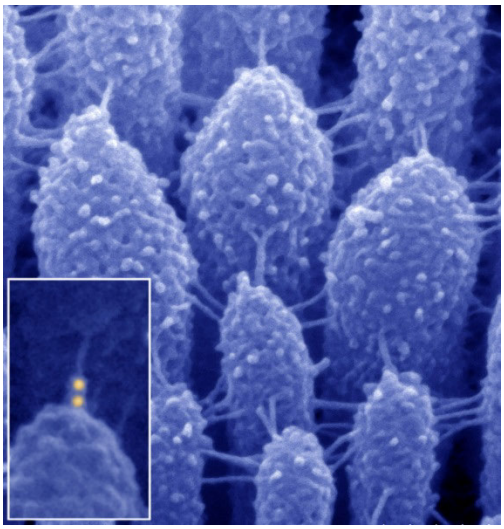

Figure 26. Scanning electron microscopy image of an inner-ear hair cell. Credit: NIDCD.

NIDCD, NICHD, and NCATS are collaborating to improve understanding and treatment of individuals with Niemann-Pick disease type C (NPC), a type of lysosomal storage disorder. Lysosomes serve as the cell's recycling centers and break down unwanted or damaged cellular contents. If lysosomes do not work properly, a buildup of cellular trash can damage or kill the cell. In NPC, fat molecules build up in the lysosomes and cause progressive neurological disease and, eventually, death. NIDCD IRP scientists are participating in Phase I and Phase IIb/III clinical trials at the NIH CC to test a promising new drug, cyclodextrin, to treat NPC.[350] The researchers are focusing on the hearing loss that results from NPC as well as additional hearing loss caused by cyclodextrin treatment. Their work will allow us to better understand how cyclodextrin causes hearing loss and how it might be prevented.

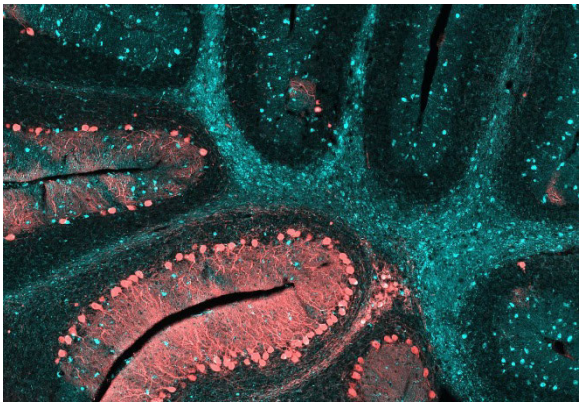

Figure 27. The cerebellum of a brain affected by NPC, a neurological disorder, at the end stage of the disease. The blue staining shows dense pockets of lipid accumulations throughout the brain that are caused by the disease. Credit: NICHD.

In FY 2015, three teams funded by NINDS, NIA, and NIGMS found that mutations in the *C9ORF72* gene that which have been found to cause amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), or sometimes both disrupt normal trafficking of molecules in and out of the nucleus of neurons,

[350] https://clinicaltrials.gov/ct2/show/NCT02534844?term=Cyclodextrin+NPC&rank=1.

causing damage.[351,352,353] Furthermore, the researchers identified molecules that are involved in the trafficking, a finding that provides insight into potential disease mechanisms and therapeutic targets. Based on an improved understanding of the *C9ORF72* mutation, also created a new mouse model of familial ALS/FTD that mimics ALS/FTD-related symptoms in humans. This new mouse model will facilitate preclinical studies and drug testing for FTD/ALS.[354]

In FY 2015, scientists at NINDS discovered that reactivation of genes that have a viral origin and are part of the human genome can cause some forms of ALS.[355] They examined brain samples from people with ALS and found that they had higher levels of mRNA and proteins encoded by the human endogenous retrovirus-K (*HERV-K*) genes compared with healthy controls. Mice genetically engineered to express one of the *HERV-K* genes developed motor neuron degeneration similar to ALS. NINDS scientists are now collaborating with the ALS Center at Johns Hopkins University to study whether antiretroviral drugs that are similar to those used to treat HIV are effective in controlling *HERV-K* replication and reversing ALS symptoms in some people with the disease.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder linked to mutations in the X chromosome and characterized by motor and cognitive impairments in older adults. NINDS, NIA, and NIDCR supported the development of a new transgenic mouse model that researchers can use to selectively induce expression of an expanded CGG repeat in the brain.[356] These mice developed intranuclear inclusions in brain tissue, a result that replicated findings in patients with FXTAS. Moreover, formation of these inclusions was reversible if expression of expanded CGG RNA was stopped at an early developmental age. This model not only allows the study of disease progression and the potential of disease reversibility, but it also suggests that early intervention might be beneficial for patients with FXTAS.

Human chromosome 21 is duplicated in DS. These duplicated regions are similar to regions on mouse chromosomes 10, 16, and 17. NINDS-supported researchers created a triple trisomic (TTS) mouse model that carries duplications of all three of these homologous regions. They examined the locomotor activity, stereotypic and repetitive behavior, anxiety, working memory, long-term memory, and synaptic plasticity of TTS mice.[357] Because the TTS mice demonstrated a number of phenotypes that are characteristic of DS, this model may serve as the new standard by which to evaluate and validate findings in other, less complete, models of DS.

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[351] Freibaum BD, et al. *Nature* 2015;525(7567):129-33. PMID: 26308899.
[352] Jovicic A, et al. *Nat Neurosci* 2015;18(9):1226-9. PMID: 26308983.
[353] Zhang K, et al. *Nature* 2015;525(7567):56-61. PMID: 26308891.
[354] Chew J, et al. *Science* 2015;348(6239):1151-4. PMID: 25977373.
[355] https://www.ninds.nih.gov/News-Events/News-and-Press-Releases/Press-Releases/Dormant-viral-genes-may-awaken-cause-ALS.
[356] Hukema RK, et al. *Hum Mol Genet* 2015;24(17):4948-57. PMID: 26060190.
[357] Belichenko PV, et al. *PLoS One* 2015;10(7):e0134861. PMID: 26230397.

Developing New Therapies for Neurological Diseases

Many NIH-funded neuroscience researchers are working to develop new therapies for neurological disorders. These interventions are designed to treat or prevent diverse problems, from diseases that cause intellectual disabilities to diseases that cause seizures (e.g., epilepsy) to other debilitating diseases (e.g., multiple sclerosis [MS], muscular dystrophy [MD]).

Status epilepticus is a seizure, or series of seizures, lasting five or more minutes. Two drugs—diazepam and lorazepam—have been shown to be effective in treating status epilepticus and are commonly prescribed. However, FDA has approved only diazepam for use in children. NIH-supported researchers set out to compare the effectiveness of the two drugs in stopping seizures in children. After a rigorous clinical trial, the scientists concluded that both drugs were equally effective and safe for treating seizures in children.[358]

Through its Bridging Interventional Development Gaps (BrIDGs) program, NCATS provides resources that investigators need to develop promising therapies for both common and rare diseases. In 2015, BrIDGs-supported researchers began exploring the antiseizure actions of a new anticonvulsant drug, 2-deoxyglucose (2DG), as a potential new therapy for epilepsy.[359] This drug acts by stopping the bursts of brain cell activity that trigger seizures.

Formerly known as the NINDS Anticonvulsant Screening Program (ASP), the Epilepsy Therapy Screening Program (ETSP) provides standardized testing in well-validated animal models of epilepsy to academic and industry researchers. The program has made important contributions to the development of several FDA-approved drugs for epilepsy that are now on the market. Following recommendations from working groups of the NINDS Advisory Council and in accordance with its new name, the program is emphasizing treatment-resistant epilepsy, as well as prevention of development and progression of epilepsy and comorbidities.

Several translational research projects have leveraged public-private funding to optimize therapy development efforts focused on the MDs, including an NINDS-funded study focused on developing the peptide biglycan as a treatment for MD. This drug was the focus of a pre–Investigational New Drug (IND) application meeting with FDA. In addition, an NINDS-funded project to develop an antisense oligonucleotide to address the toxic RNA mechanism in myotonic dystrophy was the subject of an IND application with FDA and has led to an initial clinical trial. NINDS and private funding were then used to partner with patient advocacy groups and industry in support of a multisite clinical myotonic dystrophy research network.

With support from the Michael J. Fox Foundation for Parkinson's Research, scientists from NINDS and NCATS developed a high-throughput screening test that can help find a drug that could enhance the activity of parkin, a protein whose function in the brain is abnormal in PD.[360] In healthy individuals,

[358] Chamberlain JM, et al. *JAMA* 2014;311(16):1652-60. PMID: 24756515.
[359] https://ncats.nih.gov/bridgs/projects/active/2dg-treatment-epilepsy.
[360] https://ncats.nih.gov/pubs/features/michael-j-fox.

parkin destroys faulty mitochondria, but this process is disrupted in patients with PD. Eventually, a promising candidate resulting from this process could be tested for its ability to treat the disease. In addition, the compounds identified could be used to treat several other related rare diseases.

The NCATS Discovering New Therapeutic Uses (NTU) for Existing Molecules program is designed to facilitate partnerships between pharmaceutical companies and academic researchers to advance therapeutic development. In 2015, NTU-supported researchers found that an experimental compound originally developed as a cancer therapy had the potential to be used to treat AD. In mouse models of the disease, the compound successfully reversed memory and recognition problems as well as physiological signs of the disorder.[361] Researchers are now testing the compound in humans.

There are also several new and ongoing prevention and treatment trials for AD:

- The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) trial, which began recruitment in July 2014, is testing the drug solanezumab in 1,000 volunteers with normal cognition who have enough amyloid protein in the brain to increase their risk of developing AD but who do not show symptoms of the disease.[362]
- The Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) trial assesses the safety, tolerability, and biomarker efficacy of two experimental drugs, gantenerumab and solanezumab, in people at high risk of the disease based on genetics.[363]
- The Alzheimer's Prevention Initiative apolipoprotein E (APOE) ε4 (API APOE4) trial tests two antiamyloid drugs, an active vaccine and a beta-secretase inhibitor, in older volunteers with normal cognitive function who have an increased risk of late-onset AD.[364]
- The Alzheimer's Prevention Initiative Autosomal-Dominant AD (API ADAD) is a five-year clinical trial to determine whether an antibody treatment, crenezumab, designed to bind to and possibly clear away abnormal amounts of amyloid protein in the brains of people with AD, can prevent declines in cognitive function. Crenezumab is being tested in members of a large family in Colombia who share a genetic mutation known to cause observable signs of Alzheimer's disease at around age 45. The study also includes a smaller number of U.S. participants aged 30 years and older. [365]
- Allopregnanolone Regenerative Therapeutic for Mild Cognitive Impairment (MCI) Due to AD or Mild AD is an early-phase clinical trial to evaluate the safety and tolerability of increasing doses of allopregnanolone, a natural brain steroid, over 12 weeks in treating MCI and AD. The drug has been shown to promote the generation of new brain cells, reduce amyloid levels, and restore cognitive function in preclinical animal testing.[366]

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[361] https://ncats.nih.gov/pubs/features/ntu-alzheimers-treatment.
[362] https://www.nia.nih.gov/alzheimers/clinical-trials/anti-amyloid-treatment-asymptomatic-alzheimers-disease-a4.
[363] https://clinicaltrials.gov/ct2/show/NCT01760005.
[364] https://clinicaltrials.gov/ct2/show/NCT02565511.
[365] https://clinicaltrials.gov/ct2/show/NCT01998841.
[366] https://clinicaltrials.gov/ct2/show/NCT02221622.

- Stimulating the Innate Immune System to Prevent Alzheimer's, a three-year, Phase II, proof-of-concept study is designed to evaluate for further study the use of recombinant sargramostim, a drug that stimulates the innate immune system. The study's goal is to determine whether sargramostim can clear abnormal deposits of amyloid before they cause damage and, as a result of this clearance, either prevent cognitive decline and possibly arrest or improve cognition in patients with MCI.[367]
- The Study of Nasal Insulin to Fight Forgetfulness (SNIFF) is testing an insulin nasal spray to determine whether it improves or preserves memory in adults with memory-related MCI or mild AD.[368]

NIH support of research on therapies for AD is already reaping rewards. For example, NIEHS-funded researchers studying the cancer drug bexarotene, which has been shown to reduce memory deficits in AD mouse models, found that this drug may also have promise as an AD treatment.[369] NIH-funded research has also provided evidence that antidepressants may reduce agitation in AD. Agitation, a syndrome that includes anxious, disruptive, or aggressive behavior, is common in the later stages of dementia. In a recent NIA-supported clinical trial, about 40 percent of patients with dementia receiving the antidepressant citalopram showed significant improvement in agitation symptoms compared with 26 percent of those receiving a placebo.[370] The caregivers of those receiving citalopram also reported feeling less stress. Those treated with citalopram showed some decline in cognitive and heart function. However, the researchers concluded that in light of the even greater heart health risks associated with antipsychotic treatments (the current standard treatment), citalopram may be a more effective and safer alternative for treating agitation in patients with AD.

Other NIA-supported research has shown that physical activity may help prevent hippocampal atrophy. Investigators followed the rate of atrophy of the hippocampus, a brain region that is important for learning memory, for 18 months in older adults with normal cognitive function—some of whom were at genetic risk of AD—and found that physical activity may help prevent or delay this AD-related change.[371] This study is the first to show the protective effects that physical activity may have on the hippocampus in older adults at genetic risk of AD. It also adds to past findings that physical activity, from gardening to walking and structured exercise programs, may improve cognitive function in older adults.

A large NEI clinical trial found that omega-3 fatty acid nutritional supplements did not slow AD progression in older persons. Omega-3 fatty acids are produced by marine algae and are concentrated in fish oils. Epidemiology studies suggest that regular consumption of fish, which are rich in omega-3 fatty acids, is associated with lower rates of age-related macular degeneration (AMD), cardiovascular disease, and, possibly, dementia. Although it is disappointing that these nutritional supplements do not offer the benefits for AD and AMD observed with dietary consumption of foods rich in omega-3 fatty acids, these

[367] https://projectreporter.nih.gov/project_info_description.cfm?aid=8605402&icde=36532035.
[368] https://projectreporter.nih.gov/project_info_description.cfm?aid=8800823&icde=36531722.
[369] Mounier A, et al. *J Neurosci* 2015;35(34):11862-76. PMID: 26311769.
[370] Porsteinsson AP, et al. *JAMA* 2014;311(7):682-91. PMID: 24549548
[371] Smith JC, et al. *Front Aging Neurosci* 2014;6:61. PMID: 24795624.

results provide doctors and patients with important information for evaluating the risks and benefits of taking these dietary supplements alone.

Although midlife obesity and overweight are linked to a greater risk of AD, we do not know whether these risk factors accelerate the onset of AD symptoms or are related to the severity of pathology in the brain. While analyzing data from the Baltimore Longitudinal Study of Aging (BLSA), researchers recently showed that higher adiposity at midlife (50 years of age) accelerates the age at onset of AD and is associated with more neurofibrillary tangles in the brain.[372] These findings are of considerable public health importance because they suggest that maintaining a healthy body mass index at midlife may have long-lasting protective effects and delay the onset of AD symptoms decades later.

With the National Plans to Address Alzheimer's Disease[373] as a catalyst and aided by a small award from an HHS program to encourage innovation, a cross-agency team from NIA, the Administration for Community Living, and CDC approached the challenge of increasing participation in clinical trials by bringing their aging, public health, research networks, and other resources together.[374] The effort, Recruiting Older Adults into Research (ROAR), is designed to raise awareness of and engagement in research among older adults, connect them to easy and actionable opportunities to participate, and, ultimately, expand the pool of older adults willing to participate in clinical studies and trials for AD and other health conditions. Although other health conditions will be addressed by ROAR, AD is currently the primary focus.

Restoring Nervous System Function After Injury or Disease

One of the challenges of developing therapies for nervous system disorders is that, when nerve cells die or lose their function, it is often difficult or impossible to restore that function. A properly functioning nervous system requires intricate connections that are built through a combination of embryonic development and environmental influences. Therefore, NIH also funds research aimed at restoring function after it is lost via regenerative approaches. Several updates from this field of research are described here; others are included in the "Life Stages, Human Development, and Rehabilitation" section of this chapter.

In FY 2015, NEI announced an Audacious Goals Initiative (AGI) funding opportunity to identify new factors that control neural regeneration and to compare the regenerative process among model organisms, rodents, and nonhuman primates.[375] The AGI is a bold new program to restore lost neuronal function in the retina and optic nerve due to common eye diseases, such as glaucoma and AMD.[376] As with the first round of AGI projects, which focused on novel imaging, this second round encourages interdisciplinary teams to apply and assembles grantees into a cooperative research consortium for

[372] Chuang YF, et al. *Mol Psychiatry* 2016;21(7):910-5. PMID: 26324099.
[373] https://aspe.hhs.gov/national-plans-address-alzheimers-disease.
[374] https://www.nia.nih.gov/alzheimers/features/roar-hhs-agencies-seek-recruit-older-adults-research.
[375] https://grants.nih.gov/grants/guide/rfa-files/RFA-EY-15-002.html.
[376] https://nei.nih.gov/audacious.

sharing data, methodologies, and results. This work will not only advance vision research but will also provide insights to advance the research on other neurodegenerative diseases.

NIH funds other research to repair disease-induced damage to neurons in eye diseases. Glaucoma causes damage and death of retinal ganglion cells (RGCs). These cells comprise the optic nerve and carry messages from the eye to the brain. Searching for a therapy to replace these lost cells, NIH investigators reprogramed limbal cells (adult stem cells) in the eye. They first converted these cells into pluripotent stem cells, which can turn into many other cell types, and then recapitulated natural development to create RGCs.[377] When transplanted in a rat disease model, these cells were incorporated into the host RGC layer and expressed RGC-specific markers.

In a BRAIN Initiative–supported study to create a census of every subtype of neuron, a vision research investigative team used computational tools to parse big data from molecular, functional, and new imaging methods that trace the shapes and connections of neurons in unprecedented detail. The team calculated that there are an astounding 30 different subtypes of RGCs and each subtype carries different messages about features of the visual world, such as motion or color.[378] Furthermore, when the RGC connections to the brain were damaged, as in glaucoma, some subtypes regenerated and others did not. The team identified promising molecular factors for promoting regeneration within these subtypes of cells that may unlock general principles behind neuron regeneration.[379]

Retinal degenerative diseases, such as retinitis pigmentosa and macular degeneration, destroy the light-detecting photoreceptor cells. Vision researchers, supported in part by the NIH Common Fund's Nanomedicine Initiative, designed a synthetic light-sensitive molecule, DENAQ, to induce visual responses in mouse models of retinal degenerative disease, where photoreceptor cells have died. They showed that DENAQ was incorporated and retained in retinal ganglion cells. After DENAQ injections into their eyes, blind mice responded to light impulses for several days without any toxicity.[380]

Recent advances in stem cell research present exciting opportunities for new treatment strategies in ALS.[381] In FY 2014, NINDS funded preclinical research on the potential of glial restricted progenitor cell transplantation therapy for ALS.[382] The investigators have now obtained FDA approval to test the safety of human glial restricted progenitor cells for transplantation into patients with ALS in a pair of ongoing clinical trials.[383,384]

Through the NCATS drug repurposing program, NINDS-funded researchers assessed 730 medications already in use for other disorders and identified two drugs that could activate stem cells in the brain to

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[377] Parameswaran S, et al. *Stem Cells* 2015;33(6):1743-58. PMID: 25753398.
[378] Sanes JR, et al. *Annu Rev Neurosci* 2015;38:221-46. PMID: 25897874.
[379] Duan X, et al. *Neuron* 2015;85(6):1244-56. PMID: 25754821.
[380] Tochitsky I, et al. Neuron 2014;81(4):800-13. PMID: 24559673.
[381] Richard JP, et al. *Brain Res* 2015;1607:15-25. PMID: 25223906.
[382] https://projectreporter.nih.gov/project_info_description.cfm?aid=8374970&icde=36516900.
[383] https://clinicaltrials.gov/ct2/show/NCT02478450.
[384] https://www.clinicaltrials.gov/ct2/show/NCT01348451.

stimulate myelin-producing cells and repair white matter, which is damaged in MS.[385] NINDS has recently renewed funding for this laboratory to continue to develop other forms of these drugs (e.g., injectable forms). These drugs currently have regulatory approval for use in skin creams.[386]

Collaboration and Data Sharing

NIH also funds infrastructure that supports the advancement of neuroscience research. Often, researchers can make more progress by pooling their data and resources than they could do alone. This infrastructure could include access to large datasets, biological samples or larger participant populations, or data generated by rare and expensive technologies. NIH funds a variety of such resources to help researchers maximize the impact of their science and encourage productive collaborations. Several of these collaborations are described below, and others are included in the "Research Resources and Infrastructure" section of this chapter.

NIH announced its first wave of BRAIN Initiative grants in FY 2014, and it awarded the second round of grants in FY 2015 (see the "Statement of the Director" in Chapter 1).[387] The BRAIN Initiative supports the development of a deeper understanding of the brain that will ultimately catalyze the development of new treatments and cures for devastating brain disorders and diseases.[388] To that end, the BRAIN Initiative supports the development of transformative technologies that will accelerate fundamental neuroscience research. In the first two years of the initiative, NIH supported 125 collaborative research projects led by hundreds of investigators from over 125 institutions in the U.S. and eight other countries. These investigators have already published over 100 papers. Examples of ongoing research funded by the NIH BRAIN Initiative include efforts to classify the myriad cell types in the brain, produce tools and techniques for analyzing brain cells and circuits, create next-generation human brain imaging technology, develop methods for large-scale recordings of brain activity, and integrate experiments with theories and models to understand the functions of specific brain circuits.

AD is a primary focus of the NIH Accelerating Medicines Partnership (AMP), a public-private partnership to identify and validate promising biomarkers of disease.[389] In March 2015, AMP launched its Alzheimer's Big Data Portal and concomitantly released the first wave of data through this new resource. This portal will enable sharing and analyses of large and complex biomedical datasets. This approach will make possible the development of predictive models of AD and the selection of novel targets that drive the changes in molecular networks leading to the clinical signs and symptoms of the disease.

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[385] Najm FJ, et al. *Nature* 2015;522(7555):216-20. PMID: 25896324.
[386] https://www.ninds.nih.gov/News-Events/News-and-Press-Releases/Press-Releases/Drugs-activate-brain-stem-cells-may-reverse.
[387] https://www.nimh.nih.gov/news/science-news/2014/nih-announces-first-wave-of-funding-for-brain-initiative-research.shtml.
[388] https://www.braininitiative.nih.gov/.
[389] https://www.nih.gov/news-events/news-releases/nih-led-effort-launches-big-data-portal-alzheimers-drug-discovery.

To expedite research on brain disorders, NIH coordinates a Web-based resource for sharing postmortem brain tissue. In the NIH NeuroBioBank initiative,[390] five brain banks collaborate in a tissue-sharing network for the neuroscience community.[391] Another collaboration of note is BrainSpan, a comprehensive 3D atlas of the developing human brain that incorporates gene activity, anatomical reference atlases, and neuroimaging data. Researchers involved in this initiative released their first major report in 2014.[392] This NIMH-funded resource, which is available free to the public, may enable researchers to answer questions related to the early roots of brain-based disorders, such as autism spectrum disorder (ASD) and schizophrenia.[393,394]

The Human Connectome Project's (HCP's) Blueprint Grand Challenge, supported by NIH, is an ambitious effort to map the neural pathways that underlie human brain function.[395,396] This project is leading to major advances in imaging resolution and, consequently, to a better understanding of the development and structure of the brain. In FY 2014, one group of HCP researchers reported on what may be the secret to the human cortex's exponential growth.[397] Another team explained findings linking brain connectivity to measures of personal success.[398,399] During Phase II (2012–2015), high-throughput, production-mode operations enabled data acquisition from the entire cohort of HCP participants across three sites. The HCP research, supported by NIMH, NEI, NIA, NIAAA, NIDA, and NINDS, was extended to study abnormal brain circuits in many neurological and psychiatric disorders.[400]

In FY 2014, NIMH launched the Connectome Coordination Facility[401] with the goal of maintaining a central data repository for HCP data. This facility also created a help desk service to answer questions from investigators who are trying to collect data that are compatible with the existing HCP data. Finally, the facility serves (in a limited capacity) as a quality control monitor for new data that are being deposited.

The Epilepsy Centers Without Walls initiative (CWOW) supports multicenter, multidisciplinary consortia to solve challenges in the prevention, diagnosis, or treatment of epilepsy. The first center to launch, the Epi4K Consortium supported by NINDS, has focused on identifying genetic contributors to more common forms of epilepsy by analyzing the genomes of 4,000 patients with epilepsy and their families collected by several major research groups around the world. Already, the Epi4K Consortium has found new gene mutations associated with infantile spasms and Lennox-Gastaut syndrome. These severe

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[390] https://neurobiobank.nih.gov/.
[391] https://www.nimh.nih.gov/news/science-news/2013/neurobiobank-gives-researchers-one-stop-access-to-post-mortem-brains.shtml.
[392] Miller JA, et al. *Nature* 2014;508(7495):199-206. PMID: 24695229.
[393] http://www.brainspan.org/.
[394] https://www.nimh.nih.gov/news/science-news/2014/nih-funded-brain-atlas-offers-clues-to-psychiatric-disorders.shtml.
[395] http://www.humanconnectomeproject.org/.
[396] https://www.neuroscienceblueprint.nih.gov/connectome/.
[397] Pollen AA, et al. *Cell* 2015;163(1):55-67. PMID: 26406371.
[398] Smith AM, et al. *Nat Neurosci* 2015;18(11):1565-7. PMID: 26414616.
[399] https://www.nimh.nih.gov/news/science-news/2015/our-brains-secrets-to-success.shtml.
[400] https://grants.nih.gov/grants/guide/pa-files/par-14-281.html.
[401] http://www.humanconnectome.org/

forms of childhood-onset epilepsy are difficult to treat and are associated with intellectual and developmental disabilities. The second CWOW focuses on sudden unexpected death in epilepsy (SUDEP). SUDEP is more common than sudden death in the general population, and developing treatments for this disease or modifying its course is more challenging. The Consortium is focusing on understanding the mechanisms underlying autonomic, cardiac, and respiratory dysfunction that probably contributes to SUDEP. The Consortium is also working to identify biomarkers to predict which people are at risk of SUDEP. In FY 2015, NINDS issued an RFA for a third CWOW.[402]

The Blueprint Neurotherapeutics Network (BPN) 2.0 is part of the NIH Blueprint for Neuroscience Research, a cooperative effort among the 15 NIH IC and OD offices that support neuroscience research (NINDS, NCCIH, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, and OBSSR). Established as a bridge between academic and industry drug development research, BPN 2.0 is a follow-up to BPN (FY 2011–2013), which included 15 projects that entered at the medicinal chemistry stage. BPN 2.0 offers neuroscience researchers a "virtual pharma" to develop promising hit compounds (potential drug candidates) from chemical optimization through Phase I clinical testing. Researchers in the program receive funding to conduct biological testing, access to a full range of industry-style drug development services and expertise, and control of the intellectual property for drug candidates. In FY 2015, one research team initiated studies that will enable the team to file an FDA IND application to study the lead compound in human clinical trials as a treatment for MCI. Two additional projects completed medicinal chemistry optimization and identified drug candidates that show promising activity in preclinical disease models as well as other properties that are desirable for a drug.

In response to a recommendation from the 2012 NINDS Stroke Research Priorities Meeting, NINDS established a national stroke trials network to develop, promote, and conduct high-quality, multisite clinical trials more efficiently to test promising interventions in stroke prevention, treatment, and recovery.[403] Through prioritization of research questions, harmonization and sharing of data collected in trials, and research training opportunities, the interdisciplinary network will provide expertise and infrastructure for NIH-sponsored stroke clinical trials and build research capabilities that match scientific opportunities across the spectrum of stroke research. During FY 2014 and 2015, the network became operational and initiated the first trials. It is currently conducting stroke trials in all areas (i.e., prevention, treatment for ischemic and hemorrhagic stroke, and recovery).

NINDS supports the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), which offers shared neurology expertise and infrastructure for early-stage, Phase II clinical trials, including support for patient recruitment, protocol-development assistance, and a central institutional review board (IRB).[404] The network ensures broad access to these resources for testing new therapies in development by carrying out trials in partnership with industry, foundations, or academia. The network will enable more informed decisions about which treatments to move into later-stage Phase III trials. Five studies are currently underway in NeuroNEXT; one is identifying biomarkers for spinal muscular atrophy, and

[402] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-16-012.html.
[403] https://www.nihstrokenet.org/.
[404] https://www.neuronext.org/projects.

the others are testing new therapeutic regimens for progressive MS, myasthenia gravis, severe stroke, and Huntington's disease (HD).

NINDS also funds the Neurological Emergencies Treatment Trials (NETT), a national network of centers that conduct clinical trials of treatments for neurological conditions that are commonly treated in the emergency room. NETT is similar to NeuroNEXT in that the network uses shared infrastructure and streamlined mechanisms to maximize efficiency and expedite patient recruitment into clinical trials. However, NETT is specialized in conducting late-stage (mostly Phase III) trials in prehospital and emergency room settings, which are complex due to special considerations regarding patient consent and the requirement for collaboration across medical disciplines.[405,406] A completed NETT trial, the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), was a major advance for epilepsy that was awarded the David Sackett Trial of the Year award by the Society for Clinical Trials. NETT was evaluated in FY 2015.[407] NETT received an overall positive review, and the decision was made to merge NETT's efforts with those of NHLBI and DoD to create a broader emergency research network, the Strategies to Innovate Emergency Care Clinical Trials Network (SIREN).

Large observational studies, now underway, will provide critical information to improve clinical care for TBI and clinical trials of interventions. These studies include the Transforming Research and Clinical Knowledge in TBI (TRACK TBI) study of adults and children with TBI at 11 sites in the U.S., and the Approaches and Decisions for Acute Pediatric Traumatic Brain Injury trial, which is focused on 1,000 children with severe TBI.[408] Both of these studies are part of the continuing International TBI Research Initiative in coordination with the European Union and the Canadian Institutes of Health Research. These studies use the NINDS TBI Common Data Elements, developed with other federal agencies and the international research community, and the Federal Interagency TBI Informatics Research (FITBIR) Informatics System led by NIH and DoD to encourage sharing of data.

Chronic traumatic encephalopathy (CTE) is a serious neurodegenerative disease that can result from repeated concussions. In FY 2014, NINDS released an FOA for a major longitudinal study to characterize and develop tools to diagnose CTE in living people; such diagnoses are not yet possible.[409] NIH is also working closely with the Foundation for the National Institutes of Health (FNIH) Sports and Heath Research Program to launch major cooperative projects to define the scope of long-term changes that occur in the brain years after a head injury or multiple concussions. This program has developed and validated pathological criteria to definitively identify CTE in brains on autopsy, and this research has provided the groundwork for significant new studies of CTE.

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[405] https://nett.umich.edu/.

[406] https://projectreporter.nih.gov/project_info_details.cfm?aid=8856666&icde=36493795&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball.

[407] https://www.ninds.nih.gov/sites/default/files/NETT_program_evaluation_508C.pdf.

[408] https://tracktbi.ucsf.edu/.

[409] https://grants.nih.gov/grants/guide/rfa-files/rfa-ns-14-012.html.

The Neurobiological Predictors of Huntington's Disease (PREDICT-HD) is an international 32-site observational study of individuals who are at risk of HD but do not yet show symptoms.[410] Since 2001, the project has collected clinical and genotype data and biospecimens from 800 participants with HD but no symptoms and 200 healthy volunteers. All of these data are available at BioSEND (the NINDS biomarker repository) and through dbGaP (see the "Research Resources and Infrastructure" section of this chapter). [411] In FY 2015, NINDS funded 10 ancillary studies that use PREDICT-HD biospecimens, imaging, and clinical data with the goal of discovering new biomarkers for HD.[412]

In FY 2015, the Genetic Modifiers of Huntington's Disease (GeM-HD) consortium identified genetic variations that can hasten HD onset by up to six years.[413] The group is now expanding the analysis to include data not only from individuals diagnosed with HD but also from those without symptoms who are still at risk of HD. The goal to identify the genes causing the acceleration of onset. These genes will provide important clues for developing rational treatments that delay or prevent the pathogenic process of HD. The consortium was supported by NINDS, NHGRI, and private funding.

NIEHS funded four Centers for Neurodegeneration Science to advance our understanding of environmental factors and gene–environment interactions that affect neurodegenerative diseases, including PD, and to help create new approaches to prevent and treat these diseases.[414] Teams of top scientists from different disciplines collaborate to examine the root causes of neurodegenerative diseases. Researchers at the Centers for Neurodegeneration Science are examining how exposure to pesticides, metals, tobacco smoke, and other chemicals affect the development of neurodegenerative diseases.

Guiding the Neuroscience Field and Convening Experts

NIH shows leadership in working to identify new frontiers, major opportunities, unmet needs, and evidence gaps in the neuroscience field. By convening experts, engaging in strategic planning and prioritization, and supporting major scientific initiatives, NIH seeks to move the field of neuroscience forward in directions that it deems most productive.

In FY 2014, the recommendations of the first AD-Related Dementias (ADRD) Summit, held in 2013, were published. These recommendations became the basis of research recommendation milestones that prioritize dementia research to achieve the goal of preventing and effectively treating AD and ADRD by 2025.[415] The milestones are included in the National Plans to Address Alzheimer's Disease[416] and serve as a guide for future research funding opportunities. In FY 2015, NINDS, in partnership with NIA and several nonprofit organizations, planned the second ADRD Summit to be held in March 2016.

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[410] Lee JM, et al. *Cell* 2015;162(3):516-26. PMID: 26232222.
[411] https://predict-hd.lab.uiowa.edu/.
[412] https://grants.nih.gov/grants/guide/pa-files/PAR-12-097.html.
[413] https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000371.v1.p1.
[414] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-13-007.html
[415] Montine TJ, et al. *Neurology* 2014;83(9):851-60. PMID: 25080517.
[416] https://aspe.hhs.gov/national-plans-address-alzheimers-disease.

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, NIH released the first *Bypass Budget for Alzheimer's and Related Dementias*, for FY 2017, on July 27, 2015. Strategic planning efforts informing the development of this budget included 2012 and 2015 AD Research Summits, the aforementioned 2013 ADRD Summit, and the 2013 Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome meeting.

In recent years, substantial additional funding has been directed to research on AD. The additional funds have been used to support:

- Cutting-edge research to accelerate the identification of new risk and protective genes
- Research to provide new cellular models of AD and enable rapid screens of hundreds of thousands of molecules for potential therapeutic agents
- Research on the use of new induced pluripotent stem (iPS) cell methods to obtain insights into genetic and molecular processes of AD
- Research on immune and inflammatory mechanisms contributing to or mediating the development and progression of AD
- Application of cutting-edge systems and network biology approaches to integrate multidimensional human omics (genomic, epigenomic, RNA sequencing, proteomic) data with clinical and pathological data to discover novel therapeutic targets for AD and gain a systems-level understanding of the gene, protein, and metabolic networks within which these novel targets operate
- Grants to small businesses to support translational and clinical research to develop and test therapies
- Establishment of translational centers that will develop and apply quantitative systems pharmacology (QSP) approaches to AD drug discovery and development
- Studies to speed the testing of therapies in people with the highest risk of the disease

Marijuana and Cannabinoids: A Neuroscience Research Summit, convened in March 2015 at NIH, focused on the neurological and psychiatric effects (both adverse and therapeutic) of marijuana, other cannabinoids, and the endocannabinoid system. The goal of this summit was to ensure that evidence-based information is available on the recreational and medicinal use of marijuana to inform practice and policy within a rapidly shifting landscape. The meeting was sponsored by NIDA, NIAAA, NCCIH, NIMH and NINDS.[417]

NINDS held the Parkinson's Disease 2014: Advancing Research, Improving Lives conference,[418] which mapped out the challenges and priorities for the road ahead. Conference participants developed 31

[417] https://www.drugabuse.gov/news-events/meetings-events/2016/03/marijuana-cannabinoids-neuroscience-research-summit.
[418] https://www.ninds.nih.gov/About-NINDS/Strategic-Plans-Evaluations/Strategic-Plans/Parkinsons-Disease-2014-Advancing-Research.

recommendations that will guide ongoing and future efforts in basic, translational, and clinical research to find new treatments or a cure for PD.

Life Stages, Human Development, and Rehabilitation

The goal of NIH life stages, human development, and rehabilitation research is to enable individuals to live a full life with the best health and function at every life stage. Biological processes and physical and psychosocial factors in the environment interact to shape an individual's health and functional capacities from the earliest formation of cells, tissues, organs, and organ systems through childhood, adulthood, and old age. Human development progresses most rapidly during gestation and early childhood, but it continues throughout the course of life. Each developmental stage lays the foundation for health or illness in subsequent stages.

Understanding complex developmental pathways to health or illness throughout the life course is critical to creating new ways to prevent disease and disability before they become symptomatic, preempting the disease process before it starts, or helping patients cope with injury and chronic conditions that occur. Basic, clinical, and translational research rests on the fundamental concept of developmental science: that the formation and function of cells, tissues, organs, organ systems, and the fully formed individual are sensitive to protective or harmful environmental factors, especially at certain stages. These factors include physical agents, such as industrial and agricultural chemicals; tobacco, alcohol, and other drugs of abuse; microbial infections; nutritional deficits; and even medical treatments, such as pharmaceuticals and radiation. Powerful environmental influences also include behaviors of individuals and of those with whom they live or work, as well as norms and values of households, families, schools, workplaces, and communities. Sex and gender differences affect developmental trajectories and disease risks. All such factors can have immediate, intermediate, and/or long-term effects on human health and function.

This area of NIH research also encompasses medical rehabilitation, including circuit plasticity and tissue regeneration, to optimize the functioning of individuals with disabling conditions. Medical rehabilitation research is the study of physiologic mechanisms; methods of treatment; and devices that improve, restore, or replace underdeveloped, lost, damaged, or deteriorated function. A key aspect of medical rehabilitation research is its focus on the effects of functional problems on the whole person, rather than a single organ system. Thus, researchers in this field view the individual in the context of a dynamic system of interacting variables, including biological, psychosocial, and environmental factors.

Summary of NIH Activities

The role of developmental processes in the risks of common and rare disorders and in rehabilitation science means that the scope of NIH research on life stages, human development, and rehabilitation is quite broad. NIH activities in this area include basic research on molecular and cellular processes to gain insights into the trajectories of human development, injury response, disease, and aging, as well as to

harness developmental processes for therapeutic and rehabilitative purposes. Additional research in this area includes the collection and analysis of data over the lifespan or over a specific period of interest, such as childhood or older age. Such studies can suggest the relative contributions to health or to specific disorders of environmental exposures and ongoing developmental and disease processes. Also included are studies of specific disorders, with an emphasis on an individual's life stage or developmental status.

Research on life stages and human development is supported by several ICs. NICHD, the IC with statutory responsibility for child health and human development research, conducts and supports research programs in reproductive health and in the developmental processes that begin before conception and continue through adolescence. NIA conducts and supports research on the maintenance and loss of functions during the aging process, diseases associated with aging, and the needs of older individuals and their caregivers. NINR supports research across all life stages to build the scientific foundation for clinical practice and managing and eliminating symptoms caused by illness, and it is the designated lead IC for end-of-life research. Researchers supported by NIEHS are working to increase knowledge of how certain diseases or conditions originate during critical windows of development.

Numerous other ICs support life stages, human development, and rehabilitation research in cancer, cardiovascular disease, diabetes, addiction, mental health, musculoskeletal and neurological disorders, and other areas relevant to their missions. ORWH, among its many roles, works with all ICs to develop and support opportunities for research and training in the study of disorders relevant to women's health across the lifespan and sex and gender differences in disease. Mission-specific rehabilitation research is supported by multiple ICs, including NEI, NHLBI, NIA, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, and NINDS.

Human Development

NIH scientists continually expand our understanding of how development typically progresses at the fundamental molecular and cellular level, what goes awry and why, and how health is affected.

In this vein, NIH supports research on emerging autoimmune diseases. For example, researchers funded by NIAID have identified a new immune disorder—*DOCK2* deficiency—named after the mutated gene that is responsible for the disease. An international team of collaborators studied five children, four boys and one girl, from different ethnic backgrounds who had experienced debilitating infections early in life. The children were diagnosed with combined immunodeficiency (CID), a group of inherited disorders distinguished by defects in immune system cells called T cells. CIDs also may affect other cells of the immune system, including B cells.[419]

NIAID IRP researchers have also discovered a new genetic disorder characterized by combined immunodeficiency, severe autoimmunity, and developmental delay. Genetic analysis identified the cause as loss-of-function mutations in the *TPPII* gene. Impaired *TPPII* function disrupts cellular

[419] Dobbs K, et al. *N Engl J Med* 2015;372(25):2409-22. PMID: 26083206.

metabolism, reducing glycolysis and impairing the production of effector cytokines, including interferon-γ and interleukin-1β. Thus, *TPPII* controls the balance between intracellular amino acid availability, lysosome number, and glycolysis—a balance that is vital for immunity and neurodevelopmental health.[420]

NIDCR invests in research to understand the genetic changes that underlie craniofacial disorders. For example, Van der Woude Syndrome is the most common syndromic cause of cleft lip and palate, meaning that this facial abnormality is just one piece of a broader disorder that also affects the teeth, heart, brain, and limbs. NIDCR-funded scientists have shown for the first time that Van der Woude Syndrome is associated with variations in the grainyhead-like 3 (*GRHL3*) gene.[421] Additional studies in mice and fish support the link between *GRHL3* and Van der Woude syndrome and offer new insights into facial development and craniofacial disorders.

The structures that comprise the face and skull come primarily from a specific cell type (cranial neural crest cells) during embryonic development. The behavior and properties of these cells are the result of the activity of genes that are, in turn, controlled by genetic sequences knowns as *enhancers*. After employing iPS techniques to derive cranial neural crest cells, NIDCR-funded researchers used state-of-the-art epigenomic approaches to identify, map, and duplicate these enhancer elements.[422] These studies will help identify the gene regulatory differences between humans and their nearest primate relatives that give each species its distinctive facial shape.

The placenta may be the least-understood human organ. The Human Placenta Project is a collaborative research effort that aims to understand a critical determinant of human development and health—the placental membrane that surrounds and nourishes the fetus and affects maternal health.[423] The human placenta is now the focus of a major NICHD initiative to spur development and studies of new technologies and methods for safely studying the placenta's structure and function in real time throughout pregnancy. Since 2014, NICHD has been issuing FOAs to stimulate this research and hosting annual meetings at which scientists share progress and identify emerging research opportunities.[424] An early result is the creation of placenta-on-a-chip technology; its first successful test enabled scientists to evaluate the transfer between maternal and fetal cells of glucose, a substance created when the body converts carbohydrates to energy.[425] This system has the potential to improve the fundamental understanding of the human placenta and lays the groundwork for future studies exploring the potential of organs-on-chips technology (additional tissue chip updates are presented in the "Technology Development" section of this chapter).

Gestational diabetes mellitus (GDM) increases the risk of adverse pregnancy outcomes (e.g., very large babies, elevated insulin levels in the baby). These mothers have a higher risk of developing type 2

[420] Lu W, et al. *Cell* 2014;159(7):1578-90. PMID: 25525876.
[421] Peyrard-Janvid M, et al. *Am J Hum Genet* 2014;94(1):23-32. PMID: 24360809.
[422] Prescott S, et al. *Cell* 2015;163(1):68-83. PMID: 26365491.
[423] https://www.nichd.nih.gov/research/HPP/Pages/default.aspx.
[424] https://www.nih.gov/news-events/news-releases/nih-announces-415-million-funding-human-placenta-project.
[425] Lee J. et al. *J Matern Fetal Neonatal Med* 2016;29(7):1046-54. PMID: 26075842.

diabetes in the 5 to 10 years after giving birth, and their children have an increased risk of obesity and diabetes. Results from the NICHD-led Hyperglycemic and Adverse Pregnancy Outcome (HAPO) study suggested that, in pregnant women, elevated blood glucose levels even below levels used to diagnose GDM are associated with adverse pregnancy outcomes. The HAPO Follow-Up Study (FUS), cosponsored by NIDDK and NICHD, is an observational study leveraging the HAPO participant population to determine whether hyperglycemia during pregnancy that is less severe than that in GDM also influences later levels of body fat in children and the development of diabetes in mothers after giving birth.[426] By the end of FY 2015, the HAPO FUS had recruited over 3,100 mother-child pairs from the original HAPO study; the children are now aged 8–12 years.

Genetics, environmental exposure, and development of the fetus throughout pregnancy all play a role in the incidence of birth defects. NIH research examines the types and causes of birth defects to improve understanding of their causes and treatment options. NICHD leads a multi-IC collaboration that supports basic and clinical studies on the developmental biology and genetics of structural birth defects, such as congenital heart defects, hernias, and structural brain defects.[427] Such defects affect about 4 percent of all live births in the U.S. each year. The goal of the collaboration is to develop new and valuable strategies for the molecular diagnosis, treatment, and prevention of structural birth defects.

This collaborative effort is enhanced by an NIH Common Fund initiative launched in 2015, the Gabriella Miller Kids First Pediatric Research Program.[428,429] This program is developing a resource of clinical and genetic sequence data that will allow the pediatric research community to identify genetic pathways that underlie childhood cancer and structural birth defects. Increased understanding of the underlying genetics of these conditions and discovery of previously unknown connections between seemingly disparate conditions are first steps toward developing prevention, early detection, and therapeutic interventions.

Although iodine deficiency is rare in the U.S. and Canada, it can have serious effects, including lower-than-average IQ in infants and children, decreased ability to work and think clearly in adults, and birth defects in newborns. The ODS Iodine Initiative was established in response to concerns that some pregnant women in the U.S. may have inadequate intakes of this nutrient at a time of high physiologic demand.[430] The Initiative focuses on supporting research and methodology development that can provide a scientific base for understanding how best to increase iodine levels in individuals with low to moderate risk of deficiency. An ODS publication based on the outcome of the workshops held in FY 2014 was published in 2016.[431]

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[426] http://www.hapo.northwestern.edu/.
[427] https://www.nichd.nih.gov/research/supported/Pages/bdiwg.aspx.
[428] https://commonfund.nih.gov/KidsFirst.
[429] http://grants.nih.gov/grants/guide/pa-files/PAR-15-259.html.
[430] https://ods.od.nih.gov/Research/Iodine.aspx.
[431] The results of the 2014 ODS Iodine workshops were published in September 2016 as a 14-article supplement to the *American Journal of Clinical Nutrition* [Volume 104, Number 3(S)].

Craniosynostosis, the premature closing of the sutures between the bones of the skull that restrict the growth of the skull and brain, is a common craniofacial birth defect. Surgery is currently the only treatment. NIDCR-supported researchers determined that the stem cells that give rise to the cranial bones and are involved in suture fusion reside within the suture itself rather than the layer covering the developing bone or the underlying membrane.[432] These findings may be important stepping stones toward new treatments for craniosynostosis and the use of these newly discovered stem cells in regenerative medicine.

Quickly screening newborn infants for inborn genetic disorders is essential for the early diagnosis and treatment of such disorders and to prevent or mitigate their potentially fatal or lifelong disabling effects. A key component of NICHD's efforts to increase the number of disorders that can be identified through such screening is the Newborn Screening Translational Research Network (NBSTRN).[433] Investigators turn to NBSTRN for major research tools, including a virtual repository of deidentified dried blood spots of infants undergoing state-mandated newborn screening. Another advance of note is a new whole-genome sequencing system that, when tested in acutely ill newborns, provided a clear diagnosis significantly more quickly for more than half of these infants.[434] NICHD and NIDDK grants supported this research.

Severe combined immunodeficiency (SCID), a group of rare, life-threatening, inherited immune system disorders, is caused by defects in genes involved in the development and function of infection-fighting T cells and B cells. Infants with SCID appear healthy at birth but are highly susceptible to infections. NIAID- and NICHD-supported researchers developed a test that reliably identifies infants with SCID, which allows more prompt treatment and high survival rates.[435] NIAID-funded researchers found that early transplantation of blood-forming stem cells is a highly effective treatment for infants with SCID and that earlier treatment led to better outcomes.[436] Although the standard therapy for SCID is transplantation of blood-forming stem cells, some patients lack a suitable donor. A study partially supported by NIAID showed that gene therapy using a newly engineered vector restored immunity to most of the small number of patients.[437]

NEI investigators established the value of telemedicine in diagnosing retinopathy of prematurity, a blinding complication of premature birth in which the retina is destroyed by abnormal blood vessel growth. Although fewer than 10 percent of infants require treatment, standard-of-care diagnosis depends on direct examination by an ophthalmologist in a neonatal unit. In contrast, digital retinal images can be sent electronically to trained readers at remote locations. Telemedicine offers expert diagnosis for underserved communities that lack access to expert pediatric ophthalmologists.[438]

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[432] Zhao H, et al. *Nat Cell Biol* 2015;17(4):386-96. PMID: 25799059.
[433] https://www.nbstrn.org/.
[434] Miller N, et al. *Genome Med* 2015;7:100. PMID: 26419432.
[435] Kwan A, et al. *JAMA* 2014;312(7):729-38. PMID: 25138334.
[436] Pai SY, et al. *N Engl J Med* 2014;371(5):434-46. PMID: 25075835.
[437] Hacein-Bey-Abina S, et al. *N Engl J Med* 2014;371(15):1407-17. PMID: 25295500.
[438] Quinn G, et al. *JAMA Ophthalmol* 2014;132(10):1178-84. PMID: 24970095.

Amblyopia, also known as lazy eye, is a disorder in which vision in one of the eyes is reduced because the eye and the brain do not work together properly. Amblyopia is typically treated by patching the stronger eye to foster connections between the brain and the weaker eye. Although patching is effective, it does not restore normal binocular vision in all patients. NEI researchers have developed eye exercises for the iPad that are designed to improve vision in children with amblyopia. In a clinical trial, children with recurrent amblyopia had rapid and lasting improvement in visual acuity in the weaker eye, and the benefits appear to be long term.[439] Additional updates on NIH-supported ocular research are included in the "Chronic Diseases" section of this chapter.

NIMH IRP researchers and extramural researchers funded by NIMH and NIBIB used advanced mathematical modeling techniques that combine genetic and brain imaging data to determine how genetic factors influence the thickness of the brain's outer mantle, or cortex.[440] Researchers discovered that the thickness of later-evolving and maturing areas of the cortex is increasingly influenced by genetics as the brain develops in childhood and adolescence. The areas of the brain most influenced by genetic factors are also those that are most implicated in mental illnesses, which typically emerge in late adolescence.[441] These findings may provide insight into the genetic underpinnings of certain mental illnesses.

Iron deficiency has serious consequences and, for this reason, is a public health concern. However, ensuring sufficient intakes of iron must be balanced by avoiding too much iron because excessive iron intake also has adverse effects. In 2015, ODS developed its Iron Initiative to prioritize the relevant research gaps for clarifying the benefits and harms associated with iron screening and supplementation among pregnant women and young children aged 6 to 24 months. To accomplish these goals, ODS planned a workshop, Iron Screening and Supplementation of Iron-replete Pregnant Women and Young Children to take place in FY 2016.[442]

Community water fluoridation is recognized as an effective way to prevent tooth decay. However, few studies have focused on the effects of fluoride intake on bone development in children. NIDCR researchers have collected information on fluoride intake and other factors that are potentially related to bone development from participants in a large cohort study. The researchers found no significant relationship between bone mineral measures taken at age 15 years and average fluoride intake assessed from birth through age 15 years. These results suggest that bone mineral measures in adolescence are not significantly affected by typical U.S. fluoride intakes in areas with fluoridated water during childhood and adolescence.[443]

Single or multiple environmental exposures throughout the lifespan can influence the prevalence and severity of diseases. NIH-funded researchers study the health effects of different environmental

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[439] Birch E, et al. *JAAPOS* 2015;19(1):6-11. PMID: 25727578.
[440] Schmitt JE, et al. *Proc Natl Acad Sci* 2014;111(18):6774-9. PMID: 24753564.
[441] https://www.nimh.nih.gov/news/science-news/2014/genes-impact-suspect-cortex-areas-more-as-youth-mature.shtml.
[442] https://ods.od.nih.gov/Research/Iron.aspx.
[443] Levy S, et al. *J Dent Res* 2014;93(4):353-9. PMID: 24470542.

exposures and work to identify critical windows of susceptibility during human development. To address questions at the intersection of pediatric health and the environment, NIH has renewed a major effort—first mandated by the Children's Health Act of 2000—to stimulate research on the effects of chronic and intermittent environmental exposures on child health and human development and on the underlying biological mechanisms. This effort is the successor to the discontinued National Children's Study, and multiple ICs participate as appropriate to their research missions. In conjunction with its Human Placenta Project, NICHD sought research proposals in FY 2015 for developing paradigm-shifting innovations for human placental assessment in a living body in response to environmental influences.[444] FY 2015 planning activities among multiple ICs laid the groundwork for a series of FOAs to advance the Environmental Influences on Child Health Outcomes (ECHO) Program, including FY 2016 FOAs targeted at Institutional Development Award (IDeA) states[445] to establish a pediatric clinical trials network and a network data coordinating and operations center.[446]

The Pediatric Research Using Integrated Sensor Monitoring Systems (PRISMS) program was launched in 2015 using reprogrammed National Children's Study funding.[447] This program is developing sensor-based, integrated health monitoring systems for measuring environmental, physiological, and behavioral factors in pediatric epidemiological studies of asthma and, eventually, other chronic diseases.

NIH-funded research has also shown a link between environmental exposures and brain development. One the largest pediatric MRI studies to date found a dose-response relationship between increased prenatal polycyclic aromatic hydrocarbon (PAH) exposure and later childhood reductions in the white matter surface of the left hemisphere of the brain. These reductions are associated with slower processing of information and externalizing behavioral problems, including attention deficit hyperactivity disorder (ADHD) and aggression. For postnatal PAH exposure measured at age five years, the researchers found additional disturbances in development of white matter in the dorsal prefrontal region of the brain, which is associated with concentration, reasoning, judgment, and problem-solving ability. The postnatal affects were spatially distinct and statistically independent from those for prenatal PAH exposure.[448]

NIH research is also linking certain exposures to behavioral disruption. For example, emotional and behavioral problems show up with exposure to even low levels of lead. As blood lead levels increase in children, so do the problems, according to research funded by NIEHS.[449]

Studies have shown that early-life exposure to environmental chemicals can lead to disease much later in life. Although scientists have traditionally thought that the negative effects of these exposures are reset in each generation, some casess challenge this notion and indicate that exposures can sometimes affect multiple generations. This phenomenon is known as transgenerational inheritance.

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[444] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-15-034.html.
[445] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-16-001.html.
[446] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-16-002.html.
[447] https://www.nibib.nih.gov/research-funding/prisms.
[448] Peterson BS, et al. *JAMA Psychiatry* 2015;72(6):531-40. PMID: 25807066.
[449] Liu J, et al. *JAMA Pediatr* 2014;168(8):737-45. PMID: 25090293.

The NIEHS-funded Transgenerational Inheritance in Mammals after Environmental Exposure (TIME) program funds exploratory studies that identify and characterize transgenerational inheritance after exposure to environmental toxicants, as well as mechanistic research on known examples of transgenerational inheritance. Researchers funded by TIME are using mouse and rat models to show that transgenerational inheritance occurs in these animals after exposure to environmental chemicals at environmentally relevant doses that have significant effects on human health. Their work will help reveal the genetics and biological mechanisms involved in transgenerational inheritance. Investigators are also examining whether transgenerational inheritance differs between males and females, defining developmental windows of susceptibility, and looking at possible interactions between an environmental exposure and other stressors (e.g., stress, nutrition) in stimulating transgenerational responses.[450]

NIAID-funded scientists completed a systems-level analysis of 210 healthy twins aged 8–82 years. The study encompassed 204 different parameters and found that 77 percent of them were influenced by nonheritable influences. This study suggests that the cumulative influence of environmental exposure and other factors results in the capacity of the immune system in healthy individuals to adapt to its environment.[451]

Developmental disabilities research conducted across NIH, including by multi-IC collaborations, focuses on the origins of these conditions and their early detection and treatment to optimize affected children's capacities throughout the lifespan. A growing area of research indicates that ASD may be caused by an interaction of genetic and environmental factors. The NIEHS-funded Childhood Autism Risks from Genetics and the Environment (CHARGE) study showed that global increases in duplications of rare copy number variants in genes were associated with autism.[452] CHARGE also revealed that children who lived very close to high-volume traffic early in life were more likely to have autism.[453]

A centerpiece of NIEHS' support for ASD research occurs through the Children's Environmental Health and Disease Prevention Research Centers, a joint effort of NIEHS and the EPA. The University of California at Davis Center for Children's Environmental Health and Disease Prevention (CCEH) brings together a multidisciplinary team of scientists whose mission is to identify and understand environmental, immunologic, and genetic risk factors that contribute to the incidence and severity of childhood ASD.[454] The team's work spans mechanistic studies in model systems to clinical research in human populations. The overall philosophy of CCEH is that investigation of the complex interactions of exposures and genetic susceptibility will lead to the discovery of effective intervention strategies.

NIEHS awarded eight new autism grants from two linked FOAs. The FOAs were designed to stimulate and foster research to identify environmental contributors to risk and expression of ASD and to

[450] https://www.niehs.nih.gov/research/supported/health/envepi/time/index.cfm.
[451] Brodin P, et al. *Cell* 2015;160(1-2):37-47. PMID: 25594173.
[452] Girirajan S, et al. *Hum Mol Genet* 2013;22(14):2870-80. PMID: 23535821.
[453] Volk H, et al. *JAMA Psychiatry* 2013;70(1):71-7. PMID: 23404082.
[454] http://www.ucdmc.ucdavis.edu/mindinstitute/research/cceh/index.html.

understand how environmental factors affect the underlying biologic processes implicated in ASD.[455,456] The studies that received these grants covered a range of approaches, from animal models to human epidemiology studies, and addressed diverse exposures, such as endocrine disruptors, air pollution, and diet and nutrition.

Research supported by NIEHS also revealed that DNA from the sperm of men whose children had early signs of ASD shows distinct patterns of regulatory tags that could contribute to the condition. The investigators examined the DNA in sperm obtained from the Early Autism Risk Longitudinal Investigation (EARLI) cohort. Scientists identified 193 gene sites where the presence or absence of a regulatory tag was associated with ASD. Many of these genes are related to developmental processes. The results suggest that epigenetic differences in a man's sperm may contribute to ASD risk in his child.[457]

The results of another new study reveal that most of the genetic risk for ASD comes from versions of genes that are common in the general population rather than from rare variants or spontaneous glitches. About 52 percent of the risk for autism was traced to common and rare inherited variations; spontaneous mutations were responsible for a modest 2.6 percent of the total risk.[458] Heritability also outweighed other risk factors in this study, the largest of its kind at the time of publication. Knowing the nature of the genetic risk will reveal clues to the molecular roots of the disorder. NIMH, NICHD, and NINDS collaborated on this project.

Other recent scientific advances in this area include the discovery by NICHD- and NIEHS-funded researchers that children with ASD are twice as likely as typically developing children to have been born to women who had had preeclampsia (severe high blood pressure and other anomalies), a serious pregnancy complication.[459] Another study that used fMRI study to compare brain activity in adults with and without ASD found striking differences in brain activation; these results are promising for diagnostic purposes.[460] The study was supported by NICHD and NIMH.

The architecture of the brain in a person with autism is speckled with patches of abnormal neurons, according to research funded by NIH and several private partners. Researchers found signs of disorganization in areas of the cortex that mediate social, emotional, communication, and language functions in the brains of individuals with ASD.[461] The patchy nature of the defects may explain why early treatments can help infants and toddlers with autism. Because the faulty cell layering does not occur over the entire cortex, the developing brain may have a chance to rewire its connections by sidestepping the pathological patches and recruiting cells from neighboring brain regions to assume critical roles in social and communication functions. NIMH, NICHD, and NINDS collaborated on this project.

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[455] https://grants.nih.gov/grants/guide/pa-files/PAR-14-203.html.
[456] https://grants.nih.gov/grants/guide/pa-files/PAR-14-202.html.
[457] Feinberg J, et al. *Int J Epidemiol* 2015;44(4):1199-210. PMID: 25878217.
[458] Gaugler T, et al. *Nat Genet* 2014;46(8):881-5. PMID: 25038753.
[459] Walker C, et al. *JAMA Pediatr* 2015;169(2):154-62. PMID: 25485869.
[460] Just M, et al. *PLoS One* 2014;9(12):e113879. PMID: 25461818.
[461] Stoner R, et al. *N Engl J Med* 2014;370(13):1209-19. PMID: 24670167.

Research has yielded much information on the risk factors for and the biology underlying autism. However, early diagnosis and access to effective treatment and services tailored to life stages remains a challenge for people with ASD and their families. NIMH has therefore funded 12 new research grants to develop effective, real-world–ready approaches to providing early diagnosis, treatment, and supportive services for people with ASD.[462] These grants are part of a broad research effort to provide models for the delivery of needed services to children, youth, and adults with ASD in different communities and care settings that are appropriate for each age and individual.

Eye contact during early infancy may be key to early identification of autism, according to a study funded by NIMH. Autism usually is not diagnosed until after age two, when delays in a child's social behavior and language skills become apparent. This study revealed the earliest sign of developing autism ever observed at the time of publication—a steady decline in attention to others' eyes within the first two to six months of life.[463] These results suggest that social engagement skills are intact shortly after birth in children with autism. If clinicians can identify this sort of marker for autism in young infants, interventions may be able to keep these children's social development on track.

To address unmet research needs among nonverbal children with ASD, NIDCD awarded an Autism Centers of Excellence (ACE) center grant to address why some children have limited language abilities with the goal of helping these children overcome this limitation (see Chapter 4 for a full update on the ACE program).[464] In its first few years, this ACE center has made significant progress in understanding children with minimally verbal ability who have ASD, including:

- Determining that there is no single explanation for the absence of fluent speech and language in their diverse study group
- Assessing the impact of technology, such as touch-screen computers and eye-tracking measures, on the amount of language understood by these children
- Identifying significant differences in how minimally verbal children process sounds and produce speech, which may underlie some of the language difficulties found
- Developing a promising and innovative new behavioral intervention, auditory motor mapping training, which combines the use of singing and motor activities and appears to strengthen the language regions of the brain that may be abnormal in children with ASD

NIH and several private partners funded a multiyear project to develop and improve clinical research tools for studying ASD. The project was designed to test and refine clinical measures of social impairment in ASD to better evaluate potential behavioral and drug therapies. This effort in ASD is another addition to the prestigious list of projects supported by the Autism Biomarkers Consortium for

[462] https://www.nimh.nih.gov/news/science-news/2014/new-grants-fund-cross-lifespan-services-research-for-autism-spectrum-disorder.shtml.
[463] Jones W and Klin A. *Nature* 2013;504(7480):427-31. PMID: 24196715.
[464] http://projectreporter.nih.gov/project_info_description.cfm?aid=8913120.

Clinical Trials, a large public-private partnership that aims to accelerate biomedical research progress in ASD.[465]

Rett syndrome is a neurological and developmental disorder that is associated with mutations in a gene that plays a role in nerve cell functioning and gradually slows, then stops healthy development. A small, early safety test of an experimental medication in girls with Rett syndrome found evidence that not only was the drug safe, as researchers had hoped, but it also appeared to reach the central nervous system and reduce anxiety and breathing problems, two symptoms of Rett.[466] Another study, of a repurposed cancer drug, showed promise in treating arginase deficiency, a rare, inherited disorder that causes mild to severe intellectual disability, growth deficiency, and other problems.[467] Both drug studies were supported by NICHD.

As discussed in Chapter 2, the findings of NIH-funded research are often disseminated to the public through health campaigns. One such effort is working to enhance maternal and child health by reducing the number of infants born electively very late in pregnancy and by increasing recognition of the depression that can affect women during pregnancy and in the postpartum period. Led by NICHD, the National Child & Maternal Health Education Program (a collaboration among key federal agencies and national medical, nursing, and other organizations) identified these two areas as initial priorities for outreach and public information campaigns, as well as an online continuing education course for providers. Among components of the national program are the Is it Worth It? and Know Your Terms initiatives, which aim to educate both providers and patients about the new definition of term delivery (39 weeks) and the importance of waiting until the pregnancy reaches full term to deliver the infant if neither the mother's nor her child's health is at risk.[468] The Mom's Mental Health Matters component targets information on mothers-to-be; those who have given birth; and their partners, family, friends, and clinicians. Mom's Mental Health Matters also offers an action plan and links for finding help and other information.[469]

To call attention to the physical activity and nutrition needs of individuals with intellectual, developmental, and/or physical disabilities, the 2014 White House Summit and Research Forum on Improved Health and Fitness for Americans with Disabilities convened national disability stakeholders from K-12 schools, universities, and community-based organizations as well as researchers and other subject matter experts for two days of discussions and presentations. The first day focused on sharing best practices for implementing the I Can Do It, You Can Do It! program.[470] The second day examined knowledge gaps and research opportunities in diet, physical activity, motivation, and outcomes to

[465] https://fnih.org/what-we-do/biomarkers-consortium/programs/autism-biomarkers.
[466] Khwaja O, et al. *Proc Natl Acad Sci USA* 2014;111(12):4596-601. PMID: 24623853.
[467] Burrage L, et al. *Hum Mol Genet* 2015;24(22):6417-27. PMID: 26358771.
[468] https://www.nichd.nih.gov/ncmhep/Pages/index.aspx.
[469] https://www.nichd.nih.gov/ncmhep/MMHM/Pages/index.aspx.
[470] http://www.fitness.gov/participate-in-programs/i-can-do-it-you-can-do-it/.

improve the health and life quality of all children with disabilities. The meeting was organized collaboratively by NICHD and the President's Council on Sports, Fitness & Nutrition.[471]

Life Stages

Life stages research, also commonly called life course research, is a concept that has informed landmark epidemiological and longitudinal studies. These studies linked risks of major adult-onset disorders, including type 2 diabetes, hypertension, stroke, and heart disease, to environmental influences in utero and in early childhood. The life course research model has expanded to include more developmental stages and a wide array of environmental factors and conditions of interest to determine how—and when—to intervene to prevent or treat disease.

NIH funds research on health across the human lifespan. For example, the HCP, an NIH Blueprint for Neuroscience Grand Challenge, is a consortium that conducts research on the effects of age, growth, disease, and other factors on the ever-changing connections in the human brain. Based on the success of HCP, this research was extended into the Lifespan Connectome Project (LCP) to examine the human connectome across six age groups.[472] In FY 2015, funding opportunities for LCP included the Baby Connectome Project, Developing HCP, and HCP Lifespan Aging study. Thirteen NIH ICs are jointly funding this research. Further updates on the HCP are presented in the "Neuroscience" section of this chapter.

The exposome is the measurement of the totality of exposures a person experiences from conception to death along with the associated biological responses. This concept has become increasingly important for discovering the environmental causes of disease. NIEHS funds the Emory Health and Exposome Research Center: Understanding Lifetime Exposures (HERCULES), which is conducting exposome-focused research and developing new tools and technologies for assessing the exposome.[473] This center is an important component of the NIEHS effort to transform exposure science by improving the characterization of environmental exposures; defining and disseminating the concept of the exposome; and creating the necessary tools, technologies, and research capacity to increase understanding of the exposome.

Behavioral, biological, and environmental factors can affect the health of children both during this life stage and as they grow and become adults. NIH funds research on the unique health needs of children as well as the impact of childhood health throughout the remaining stages of life.

Epidemiological evidence supports associations between prenatal exposure to environmental organic chemicals and childhood health impairments, making the ability to accurately identify and record exposures a high priority. NIEHS-funded researchers presented findings from a pilot study that used

[471] https://www.nichd.nih.gov/about/meetings/2014/Pages/100714.aspx.
[472] https://humanconnectome.org/lifespan-studies.
[473] https://emoryhercules.com/.

tooth matrix biomarkers to obtain trimester-specific information on exposures to a range of organic chemicals.[474]

As part of a trans-NIH effort to develop new tools to investigate the effect of environmental exposures on child health, NIH funded four centers in September 2015 to establish the Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium. The goal of this consortium is to test several pediatric patient–reported outcome tools that measure aspects of physical, mental, and social well-being, such as pain, anxiety, and peer relationships. The research will also help improve understanding of the effects of environmental stressors on symptoms and quality of life in children with a variety of chronic diseases or conditions. The PEPR Consortium is funded through the NIH OD and administered by the NIAMS.[475]

Nutrition is another important area of medical research. Results from a two-year clinical trial show that calorie restriction (i.e., a reduction in calorie intake without deprivation of essential nutrients) in normal-weight and moderately overweight people did not have some metabolic effects found in laboratory animal studies.[476] However, the researchers found that calorie restriction modified risk factors for age-related diseases and influenced indicators associated with longer lifespan, such as blood pressure, cholesterol, and insulin resistance.

The NIH CC has a long history of achievements that have advanced pediatric medicine. CC IRP investigators have discovered the causes and first treatments for childhood leukemia; successfully treated pediatric HIV; and spearheaded the identification, classification, and treatment of several childhood-onset psychiatric disorders. However, the full potential of the IRP pediatric physician-scientists remains untapped because the CC cannot currently provide routine support for research in infants, and IRP investigators have a limited capacity to care for very small children who are, or have an increased risk of becoming, acutely ill. The CC, in collaboration with NICHD, therefore convened a committee of NIH staff experts to create a strategic vision for pediatric research at the CC that incorporated insights from a group of extramural pediatric experts and advisors. In July 2014, the committee finalized its strategic vision. This vision identified strategic themes for pediatric research, including current obstacles and resources needed, and strategies to achieve the pediatric research goals. This strategic vision will be the focus of future CC efforts to ensure that the CC maintains its leadership in the performance of cutting-edge translational and clinical child health research and its ability to attract and retain top pediatric researchers.

Clinicians face special challenges in prescribing drugs for children who are ill because, for example, children's developing bodies often process drugs differently than adults' bodies or even those of children at different developmental stages. There is little incentive for pharmaceutical manufacturers to invest in producing the child-specific data needed for FDA to label (approve) a drug for pediatric use, however, because drugs are so widely (and legally) prescribed off label for children.

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[474] Andra SS, et al. *Environ Res* 2015;142:387-406. PMID: 26219084.
[475] https://www.niams.nih.gov/News_and_Events/Announcements/2015/PEPR_announcement.asp.
[476] Ravussin E, et al. *J Gerontol A Biol Sci Med Sci* 2015;70(9):1097-104. PMID: 26187233.

The implementation of the Best Pharmaceuticals for Children Act (BPCA),[477] led by NICHD, is resulting in extensive collaborations among NIH ICs, other federal partners, and the private sector to assess research needs and conduct needed studies. Examples of recent accomplishments include FDA labeling of sodium nitroprusside for pediatric use. This drug is commonly used to control blood pressure in both adult and pediatric patients in intensive care units.[478] A study of meropenem for preterm infants with serious abdominal infections found that the drug, already in use, is safe and not associated with serious side effects; the scientists established dosing guidelines for infants of various ages, and the drug was labeled for pediatric use.[479]

The influence of the built environment on human behavior is an important area of study for local officials managing infrastructure, traffic, and pedestrian access. A research team funded by OBSSR and NCI explored the impact of zoning code reforms on levels of physical activity.[480] The researchers developed an index for traffic calming measures and found that a higher level of traffic calming is associated with use of an active form of transportation (i.e., walking or biking) by more elementary school children to get to school.[481] This is an important finding for encouraging built environment changes that would promote physical activity among elementary school students.

As children advance into adolescence, their health needs change. NINR funded a study to examine the effects of the Creating Opportunities for Personal Empowerment (COPE) Healthy Lifestyles Thinking, Emotions, Exercise, Nutrition (TEEN) program on obesity and depressive symptoms in high-school–aged adolescents.[482] COPE is a teacher-delivered intervention program that includes lessons on common health issues for teens, physical activity, and homework assignments. This was one of the first studies to report multiple immediate improvements that were sustained over time using a teacher-delivered, cognitive-behavioral skills-building intervention program incorporated into a high school health education class. Twelve months after completing the program, students had improved health behaviors, a lower body mass index, fewer symptoms of depression or anxiety, and higher academic performance. Routine integration of such programs into health education curricula in high schools may be an effective way to prevent high-risk teens from becoming overweight or obese and could lead to improved physical health, psychosocial outcomes, and academic performance.

In FY 2015, NIH awarded 13 grants to research institutions around the country as part of the Adolescent Brain Cognitive Development (ABCD) study, the largest long-term study of brain and cognitive development in children across the U.S. The ABCD study will follow approximately 10,000 children beginning at ages 9–10 for 10 years into early adulthood to determine how a wide range of behavioral, genetic, and environmental factors interact and influence brain structure and function as well as life and

[477] https://bpca.nichd.nih.gov/Pages/default.aspx.
[478] Hammer G, et al. *Pediatr Crit Care Med*. 2015;16(5):397-403. PMID: 25715047.
[479] https://www.federalregister.gov/documents/2015/05/28/2015-12848/pediatric-studies-of-meropenem-conducted-in-accordance-with-the-public-health-service-act.
[480] https://projectreporter.nih.gov/project_info_description.cfm?aid=8900430&icde=29749869.
[481] Nicholson L, et al. *Transp Res D Transp Environ* 2014;33:17-25. PMID: 25506255.
[482] Melnyk B, et al. *J Sch Health* 2015;85(12):861-70. PMID: 26522175.

health outcomes.[483] Studies will track mental health, substance use patterns, academic achievement, IQ, cognitive skills, and many other outcomes. The study's longitudinal design will allow us to draw more meaningful conclusions and connections at the individual level between key genetic and biological factors and behavioral, social, and environmental influences during adolescence. The ABCD study was initiated by the Collaborative Research on Addiction at NIH (CRAN), a partnership of NIDA, NIAAA, and NCI), which will lead this effort with NICHD, NIMH, NIMHD, NINDS, and OBSSR.

To understand how different sets of skills change throughout the lifespan, researchers analyzed a large number of scores on types of cognitive tests taken by people of a variety of ages. NICHD-supported researchers found that processing speed—how quickly someone can manipulate digits, words, or images—generally peaked in the late teens, and memory of some things, such as names, was strongest among people in their early 20s.[484] Other memory-based skills, including the ability to recall faces and do some mental manipulation of numbers, peaked at about age 30. For another test, which involved reading strangers' moods from the expressions in their eyes, people in their 40s or 50s consistently did the best, and this skill declined very slowly later in life.

Some adult populations have different health needs and concerns than others. In 2015, ORWH sponsored a workshop on women's health issues that was jointly organized by the Committee on Population and the Board on Population Health and Public Health Practice of the National Academies of Sciences, Engineering, and Medicine.[485] The objective of the workshop was to highlight the significantly poorer health of women in the U.S than in 16 peer countries. The workshop reached across sectors, disciplines, and areas of expertise to explore what is known and what needs to be known. It identified key factors at the system, federal, state, patient, and provider levels that might explain the comparative deficiency in the health of women in the U.S. The workshop identified key research areas to decrease mortality and morbidity rates in both the short and long term. It also identified some areas in which small interventions that are relatively inexpensive could have large effects.

The death rate among middle-aged, white Americans rose significantly between 1999 and 2013, reversing a decades-long trend of improvement, according to new NIA research.[486] This population also reported worse physical and mental health than other age groups. The investigators noted that the increase in midlife mortality rates is only partly understood. Increased availability of opioid prescription drugs, chronic pain (for which opioids are often prescribed), and the economic crisis that began in 2008 may all have contributed to increases in rates of overdose, suicide, and liver disease associated with alcohol abuse.

At the other end of the life stage spectrum, NIH supports research on aging and the health and well-being of older adults. Scientists seek to understand the nature of aging and the aging process along with diseases and conditions associated with aging to extend the healthy, active years of life. Much of this

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[483] https://www.drugabuse.gov/news-events/news-releases/2015/09/nih-launches-landmark-study-substance-use-adolescent-brain-development.
[484] Hartshorne JK, et al. *Psychol Sci* 2015;26(4):433-43. PMID: 25770099.
[485] https://orwh.od.nih.gov/research/reports/raising-the-bar/.
[486] Case A, et al. *Proc Natl Acad Sci USA* 2015;112(49):15078-83. PMID: 26575631.

research is conducted by NIA, but other ICs contribute to this important research area as well. See Chapter 4 for a full update on the Claude D. Pepper Older Americans Independence Centers that are supported by NIA.

Active since 1958, the BLSA[487] is the first study to ask and attempt to answer the fundamental question, "What is 'normal' human aging?" Although there is still much to learn, BLSA findings have led to two major conclusions. First, normal aging can be distinguished from disease in that the body changes and some functions can decline over time, but these changes do not inevitably lead to disease. Second, there is no single, chronological timetable of aging. Although these two paradigms may seem like common knowledge today, they represent a radical departure from the conventional wisdom of the mid-20th century and have led to many changes in the way in which the health of older Americans has been addressed.

Another research team conducted a complementary study that showed that individuals age at different rates. Much of the research on human aging has been conducted in animal models and in older people. The Dunedin Study in New Zealand, funded in part by NIA, has taken a different approach, studying a group of 1,037 people born in 1972 or 1973 from birth to age 38.[488] Study investigators recently reported that they have found that young adults are aging at different rates. The researchers developed and validated two methods to measure aging in young adults. One method applied an algorithm of multiple biological measures, such as of blood pressure and cholesterol. Using this method, some 38-year-olds appeared to be biologically older than their peers. A second method assessed the deterioration of several organ systems (e.g., heart, lung, kidney, liver) and immune function over 12 years. The investigators also noted that these differences are correlated with various measures of earlier life exposures and experiences.

NIA-supported studies in the emerging field of geroscience, which explores the basic mechanisms by which aging influences the risk of most chronic diseases and conditions, will provide needed insight into ways to address these diseases and disorders as a group, rather than one at a time. The NIA-led GeroScience Interest Group (GSIG) involves active participation by 20 NIH ICs and is leading the effort to accelerate and coordinate efforts to promote further discoveries on the role of aging as a risk factor for disease and disability. A concept paper from the GSIG's international Geroscience Summit was published in *Cell* in November 2014, and NIA anticipates that summit recommendations will continue to guide and energize the field.[489]

ORWH and NIA fund a Specialized Center of Research on Sex Differences[490] at the Mayo Clinic that has the goal of understanding sex differences in vascular degeneration and cognitive decline. Specifically, the researchers are interested in understanding whether estrogen treatment for women during early

[487] https://www.blsa.nih.gov/.
[488] Belsky D, et al. *Proc Natl Acad Sci USA* 2015;112(30):E4104-10. PMID: 26150497.
[489] Kennedy B, et al. *Cell* 2014;159(4):709-13. PMID: 25417146.
[490] https://orwh.od.nih.gov/research/funded-research/scor/.

menopause can protect parts of the brain that are associated with cognitive health and cognitive performance.

Other research on aging used animal models. Recent studies in animals have shown that lack of SIRT3—a protein in cells' mitochondria that is active in numerous mitochondrial functions—can directly or indirectly cause or increase the severity of age-associated diseases.[491] Thus, SIRT3 deficiency may represent a new accelerated aging model that might be useful for uncovering novel pathways or molecules that regulate the aging process. In a separate study, NIA intramural researchers found that SIRT3 protects brain cells from stress in a mouse model and that normal mice that exercised on running wheels had significantly higher SIRT3 levels in hippocampal neurons than mice that did not exercise.[492] These findings suggest that bolstering mitochondrial function and stress resistance by increasing SIRT3 levels may offer a promising therapeutic target for preventing age-related cognitive decline and brain diseases.

AD and dementia become more common as people grow older, but they are not a normal part of aging. NIH-funded scientists are making great strides in identifying potential new ways to help diagnose, treat, and even prevent AD and related dementias (updates are included in the "Neuroscience" section of this chapter).

Family caregivers of individuals with dementia often experience severe stress and are at risk of poor health outcomes, including depression and anxiety, but many caregivers encounter barriers that make in-person participation in interventions difficult. These barriers can include time constraints, long distances to intervention sites, and a lack of transportation. A recent NINR study found that caregivers of people with dementia who were distressed and received a telephone-delivered intervention had significant improvements in depressive symptoms and reactions to care-recipient behavior.[493] These findings demonstrate that an intervention delivered exclusively by telephone may result in positive outcomes for distressed caregivers of people with dementia, and such an intervention may be useful for caregivers who face barriers to in-person participation.

The Health and Retirement Study (HRS),[494] NIA's flagship study of aging, will complete its first 25 years of data collection in FY 2016. In preparation for this milestone, HRS will implement several enhancements in 2016. First, HRS will add respondents representing the late Baby Boom (people born between 1960 and 1965) to maintain the study's representation of Americans aged 50 years and older. Second, HRS will field a cost-effective algorithmic approach to assessing cognitive impairment and dementia, the Harmonized Cognitive Assessment Protocol (HCAP). This protocol will provide a basis for comparing trends over time in the U.S. and in countries that have conducted HRS-like longitudinal studies of aging. Third, the study will expand the collection of objective health measures through venous blood collection, including by using assays that capture the aging of the immune system and related molecular and cellular age–related changes. This study will provide the opportunity to perform analyses

[491] Cheng A, et al. *Cell Metab* 2016;23(1):128-42. PMID: 26698917.
[492] McDonnell E, et al. *Trends Endocrinol Metab* 2015;26(9):486-92. PMID: 26138757.
[493] Tremont G, et al. *Alzheimers Dement* 2015;11(5):541-8. PMID: 25074341.
[494] http://hrsonline.isr.umich.edu/.

that will help researchers understand the aging of the immune system at the molecular and cellular levels. It also has the potential to reveal the biological pathways through which differences between social and demographic groups affect health. NIA has taken the lead in building the necessary infrastructure to facilitate the analysis of harmonized data from the HRS and similar studies around the world.

In addition to the severe medical and psychological costs to patients and their families, AD and related forms of dementia impose significant economic costs. In a recent NIA-funded study, economists found that in the last five years of life, total healthcare spending for people with dementia was more than $250,000 dollars per person, some 57 percent higher than the costs associated with death from other diseases, including cancer and heart disease. The new analysis showed that total healthcare spending was $287,000 for those with probable dementia and $183,000 for other Medicare beneficiaries in the study.

Sarcopenia, a loss of muscle mass often associated with weakness, is a commonly recognized cause of disability in older people. However, without a consensus on ways to measure this condition, the development of interventions for sarcopenia has been challenging. In 2014, the leaders of the FNIH Biomarkers Consortium Sarcopenia Project—which was conducted by scientists and grantees from NIA and NIAMS along with other partners in government, academia, and the private sector—proposed a comprehensive set of diagnostic criteria for the disease. The proposed criteria included measures, such as walking speed, grip strength, and muscle mass in the arms and legs.[495] These criteria offer a way to better define and measure this disabling condition so that researchers can eventually assess the effectiveness of drugs and other interventions for it.

NIA-supported investigators have identified a new class of drugs, senolytics, that target and kill aged, or senescent, cells in mice. The team also found that a single dose of senolytic drugs led to improvements in the animals' health and function.[496] Previous research has shown that genetically modifying mice to remove their senescent cells extended their health span (length of time they are healthy), but this study is the first to imitate the approach pharmacologically in a mouse model of extremely accelerated aging. This discovery may have a tremendous impact on quality of life and the burden of age-related chronic diseases.

In 2014, NIA also renewed support for the Interventions Testing Program (ITP), which supports the testing of compounds that have the potential to extend the lifespan and delay disease and dysfunction in mice.[497] Foods, diets, drugs, and hormones are tested through the ITP, and some compounds, such as rapamycin, have been found to increase not only the lifespan, but also mouse health.

Serious injuries from falls, such as broken bones or TBI, are a major reason for the loss of independence among older people. In 2014, NIA partnered with the Patient-Centered Outcomes Research Institute (PCORI) to support a large, multicenter clinical trial to test individually tailored interventions to prevent

[495] https://www.nia.nih.gov/news/research-consortium-including-nih-proposes-diagnostic-criteria-sarcopenia.
[496] Zhu Y, et al. *Aging Cell* 2015;14(4):644-58. PMID: 25754370.
[497] https://www.nia.nih.gov/research/dab/interventions-testing-program-itp.

fall-related injuries.[498] The award is part of the two organizations' Falls Injuries Prevention Partnership. Study participants will include 6,000 community-dwelling adults aged 75 and older with one or more modifiable risk factors for falling. This trial is scheduled to conclude in 2019.

The Investigators with the Lifestyle Interventions and Independence for Elders (LIFE) study is an NIA-funded major clinical trial comparing the effects of a moderate-intensity physical activity program with those of a health education program on prevention of mobility loss disability in at-risk older Americans. The LIFE investigators reported that a carefully structured, moderate physical activity program can reduce the risk of losing the ability to walk without assistance—perhaps the single most important factor in whether vulnerable older people can maintain their independence. The researchers found that a regular, balanced, and moderate physical activity program followed for an average of 2.6 years reduced the risk of major mobility disability by 18 percent among participants.[499]

Exercise is good for you, but which molecular changes are triggered by physical activity or how they improve the function of different tissues and organs in the body is not well understood. In FY 2015, the NIH Common Fund announced plans to fund the Molecular Transducers of Physical Activity Consortium (MoTrPAC) with administrative support from NIAMS, NIBIB, NIDDK, and NIA. The consortium's aims are to catalogue the biological molecules that change in response to exercise, identify key molecules that transmit physical activities' signals throughout the body, and begin to determine how these molecules provoke the changes associated with better health.[500] Armed with this knowledge, researchers and clinicians may one day be able to develop optimal physical activity recommendations for people at various stages of life, develop precisely targeted regimens for individuals with particular health needs, and design interventions to preserve the health of people who cannot be active due to illness or injury.

Recognizing the value of exercise based on the findings of research, such as that just described, NIA, with the U.S. Surgeon General, recently launched its nationwide Go4Life campaign. Based on an extensive body of clinical research and expert advice, this program is designed to motivate older Americans to engage in physical activity and exercise by becoming active for the first time, returning to exercise after a break in their exercise routines, or building activity into daily routines. Go4Life offers exercises, motivational tips, and free resources to help participants get ready, start exercising, and keep going. The Go4Life campaign centers on an interactive website[501] that features an evidence-based exercise guide in both English and Spanish, exercise videos, and more. The initial partners include a diverse group of public and private Go4Life team members from major health and aging organizations and agencies. In 2014, NIA redesigned the Go4Life website. With support from the White House Conference on Aging and the Robert Wood Johnson Foundation, September 2015 was designated National Go4Life Month. Over a dozen private organizations sponsored activities in support of Go4Life, and older adults joined U.S. Surgeon General VADM Vivek H. Murthy, M.D., M.B.A.; NIA Director Richard

[498] https://www.nia.nih.gov/news/nih-pcori-announce-major-award-prevent-falls-injuries-older-people.
[499] Pahor M, et al. *JAMA* 2014;311(23):2387-96. PMID: 24866862.
[500] https://commonfund.nih.gov/MolecularTransducers.
[501] www.nia.nih.gov/go4life.

Hodes, M.D.; fitness expert Donna Richardson; and leaders from several agencies and organizations for a fitness walk in the Nation's capital on September 18, 2014.

NIH supports several other initiatives designed to disseminate health research–based findings to older Americans. For example, NIHSeniorHealth.gov,[502] a joint effort of NIA and NLM, provides research-based, online health information for older adults in clear, large-print, easy-to-read segments as well as in open-captioned videos that offer simple navigation. Between FY 2014 and FY 2015, the number of page views for NIHSeniorHealth.gov remained stable at nearly 5 million, and over 1.5 million people visited the site. NINR's End-of-Life module on NIHSeniorHealth.gov contains information for older Americans and their caregivers on a myriad of questions regarding death and dying as well as on palliative and end-of-life care. The module addresses topics, such as pain and other symptoms, places and planning for end-of-life care, support for caregivers, and coping with grief.[503]

Rehabilitation

Millions of Americans have a disability so severe that they have difficulty with everyday tasks, such as going to work or taking care of themselves. Disabilities can occur as a result of injury, age, or genetic or environmental factors. Rehabilitation research explores the intricate biology of disabilities, seeks ways to help restore lost function, and strives to help people with disabilities reach their full potential. NIH support for rehabilitation medicine benefits individuals with temporary or chronic limitations in physical, cognitive, or sensory function that require rehabilitation.

Seventeen NIH ICs fund rehabilitation research. NIH awarded $494 million in FY 2014 and $514 million in FY 2015 to support rehabilitation research conducted by investigators in universities, nonprofit institutions, and small businesses.[504] This portfolio encompasses the full range of biomedical, behavioral, and social sciences research from basic to applied.

The primary aims of rehabilitation research at NIH are to improve rehabilitation and habilitation approaches for individuals with disabilities and to gain knowledge about diseases that cause disability. Rehabilitation research includes the study of mechanisms, interventions, and methods that improve, restore, or replace lost, underdeveloped, or deteriorating function in people with disabilities in the context of their environment. Function includes a person's use of body systems, ability to complete activities and participate in society, and satisfaction with quality of life.

A focal point for this research is NICHD's National Center on Medical Rehabilitation Research (NCMRR),[505] which emphasizes the rehabilitation and lifelong care of people with physical disabilities resulting from developmental disorders, injury (e.g., stroke, spinal cord injury), musculoskeletal disorders, and aging and degenerative conditions. Through basic, translational, and clinical research,

[502] This website was retired in 2017. Some similar information can be found on the Health and Aging section of the NIA Web site.
[503] http://nihseniorhealth.gov/endoflife/preparingfortheendoflife/01.html.
[504] https://report.nih.gov/categorical_spending.aspx.
[505] https://www.nichd.nih.gov/about/org/ncmrr/Pages/overview.aspx.

NCMRR aims to foster development of scientific knowledge needed to enhance the health, productivity, independence, and quality of life of people with physical disabilities.

One important area of rehabilitation research is in regenerative medicine, which is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. This field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves. Regenerative medicine also empowers scientists to grow tissues and organs in the laboratory and safely implant them when the body cannot heal itself.

Several ICs conduct regenerative medicine research that pertains to their mission. For example, NIDCR facilitates clinical translation of the most promising scientific and technological advances to regenerate and reconstruct dental, oral, and craniofacial (DOC) tissues. In 2015, NIDCR launched a new effort to develop the multidisciplinary DOC Tissue Regeneration Consortium (DOCTRC), which will conduct preclinical studies leading to submission of new drug and device applications.[506] NIDCR expects this work to result in safe and effective clinical strategies for the regeneration of functional tissues of the human DOC region. These tissues include vascularized and innervated craniofacial bone, musculoskeletal complex, periodontium, tooth, cartilage, salivary gland, and temporomandibular joint.

Nerves control the function of many organs, and damage to the nerves leads to organ degeneration and loss of function. In 2015, NIDCR intramural scientists discovered that the nerves controlling saliva production produce factors that promote the growth of stem cells in the gland.[507] They also found that growth factors made by the stem cells support nerve growth.[508] These growth factors can improve gland regeneration after tissue damage, such as that resulting from radiation to treat head and neck cancer. Ongoing research will determine whether certain factors that improve nerve function help enhance salivary gland regeneration after radiation damage. Additional updates on regenerative neuroscience research are available in the “Neuroscience” section of this chapter.

In a seminal study, NIDCR-supported investigators identified a population of highly enriched postnatal skeletal stem cells in mouse bone marrow and found that subsets of this population have varying potential to form bone, cartilage and connective tissue.[509] The next step in this research is to identify similar stem cell subsets from human bone marrow. Such an accomplishment could lead to the development of a new generation of therapeutic approaches for the regeneration of skeletal tissues.

The sugars that coat the surface of all cells have an important role in controlling how growth factors bind to and signal through receptors on cells to change cell functions. In 2014, NIDCR intramural researchers discovered that specific sugar structures control interactions with the fibroblast growth factors (FGF) that are important for stem cells to function in salivary glands.[510] Ongoing research may

[506] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-15-005.html.
[507] Knosp W, et al. *Dev Cell* 2015;32(6):667-77. PMID: 25805134.
[508] Nedvetsky P, et al. *Dev Cell* 2014;30(4):449-62. PMID: 25158854.
[509] Chan C, et al. *Cell* 2015;160(1-2):285-98. PMID: 25594184.
[510] Patel V, et al. *Dev Cell* 2014;29(6):662-73. PMID: 24960693.

identify mimics of these sugar structures that can improve the growth of stem cells during repair and regeneration of salivary glands.

Prosthetics are also an important area of rehabilitation research. Although modern prosthetics have become lighter and more flexible, they cannot reproduce the power that human muscles generate in able-bodied individuals. Powered prostheses, or robotic legs, have motors to generate force, but they lack the intelligence to respond stably to disturbances or changing terrain. However, NIH-supported bioengineering researchers have now developed and successfully tested a control model that adapts an approach from two-legged robots. In tests of the new device, three individuals with amputation were able to walk using the leg at variable rates (steps per minute) on a treadmill.[511] This approach to prosthetics may enhance mobility and quality of life after amputation or after a stroke or spinal cord injury.

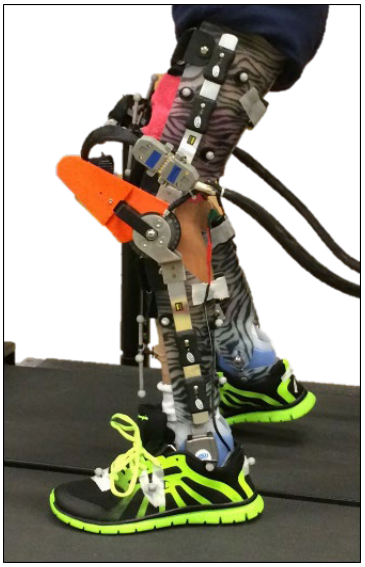

Figure 28. Robotic exoskeleton developed by researchers from the NIH CC's Rehabilitation Medicine Department. Credit: NIH CC.

In another study funded by NINR, researchers designed a lightweight ankle exoskeleton that harnesses the power of a person's own muscles to make walking more efficient.[512] This device requires no external power and uses a spring system instead to reduce the load placed on the calf muscles and make walking easier. The researchers tested the devices in nine healthy adults who wore them on both legs while walking on a treadmill. These experiments revealed that wearing the exoskeleton reduced the energy cost of walking by 7.2 percent, which is equivalent to the effect of taking off a 10-pound backpack. Although the exoskeleton is in the prototype phase, it holds promise for making walking easier for people recovering from an injury or dealing with the effects of normal aging.

Electrical stimulation is another tool that has applications for rehabilitation and therapy for persons with disabilities. In FY 2015, the NIH Common Fund launched the Stimulating Peripheral Activity to Relieve

[511] Gregg R, et al. *IEEE Trans Robot* 2014;30(6):1455-71. PMID: 25558185.
[512] Collins S, et al. *Nature* 2015;522(7555):212-5. PMID: 25830889.

Conditions (SPARC) program.[513] SPARC is designed to explore the peripheral nerve control of a variety of organs to catalyze the development of therapies based on precise stimulation of peripheral nerves. These neuromodulation therapies hold great promise for treating a variety of conditions, such as heart failure, hypertension, gastrointestinal disorders, and type II diabetes. SPARC will lay the scientific foundation for the public and private research communities to design and implement effective and minimally invasive therapies and rapidly advance this new approach to treating disease.

Researchers funded by NIBIB, NINDS, NICHD, and NCATS continue to investigate the use of electrical stimulation to the spinal cord to help people paralyzed by spinal cord injury. In addition to an implantable stimulator, NIH-supported researchers began developing a strategy for delivering stimulation to the spinal cord noninvasively in the belief that this approach could greatly expand the number of individuals with paralysis who could benefit from spinal stimulation. Five men with complete motor paralysis were able to voluntarily generate step-like movements thanks to the new strategy. After just four weeks of receiving stimulation and physical training, the men were able to double their range of motion when voluntarily moving their legs while receiving stimulation.[514] As they continue to move the field forward, three groups of researchers supported by NINDS and NIBIB have received BRAIN Initiative funding from the Defense Advanced Research Projects Agency (DARPA) to build on the fundamental discoveries that were made possible by NIH support for research on enhancing neural prosthetics to sense touch and movement realistically.[515]

Another research team is investigating how to improve motor activity and increase residual strength in individuals with spinal cord injury. NICHD-supported scientists completed a feasibility and proof-of-principle study to investigate the effectiveness of anodal transcranial direct current stimulation (a-tDCS), a treatment that has shown promise in patients with stroke. The researchers administered a-tDCS interventions at different intensities and targeted upper-limb muscles with diminished motor output in individuals with chronic spinal cord injury. The researchers found that a-tDCS was a safe and effective method for enhancing corticospinal excitability, and it may help improve motor activity.[516]

It is estimated that more than 46 million people in the U.S. have some form of disordered communication. NIDCD supports research on rehabilitation and interventions for persons with hearing loss, speech impairment, and other communication disorders. NIDCD-supported voice scientists, in collaboration with other NIH-supported researchers, have bioengineered vocal fold tissue in the laboratory using human cells.[517] The tissue had physical qualities that allowed it to behave in the same way as normal vocal fold tissue. To determine whether it could transmit sound, the researchers transplanted the tissue into an animal model. The bioengineered tissue performed well and was not rejected by the recipient, which is usually a major obstacle in these types of surgeries. This proof-of-

[513] https://commonfund.nih.gov/sparc.
[514] Gerasimenko Y, et al. *J Neurotrauma* 2015;32(24):1968-80. PMID: 26077679.
[515] https://www.ninds.nih.gov/News-Events/News-and-Press-Releases/Press-Releases/NIH-funded-research-lays-groundwork-next.
[516] Murray L, et al. *Arch Phys Med Rehabil* 2015;96(4 Suppl):S114-21. PMID: 25461825.
[517] Ling C, et al. *Sci Transl Med* 2015;7(314):314ra187. PMID: 26582902.

principle study provides hope that individuals who can no longer use their voice because of loss of their laryngeal tissue will one day have better treatment options.

Another NIDCD project supports research designed to improve understanding of the underlying neurobiology of language impairments, such as aphasia, the language problem typically associated with stroke. Using neuroimaging techniques, scientists identified new brain areas associated with aphasia. In one study, scientists discovered that different areas of the brain control word and sentence comprehension in primary progressive aphasia instead of a single area as was previously thought.[518] In another study, researchers used neuroimaging combined with behavioral assessment in individuals with aphasia to match brain lesions with corresponding symptoms.[519] The results helped scientists learn more about symptom diversity in individuals with language impairments, and the newly identified neural areas can serve as targets for diagnosis and treatments.

A new mini inner-ear drug delivery device could help with common hearing and balance problems. NIDCD-supported scientists used microfluidic and microelectromechanical systems technologies to develop a miniaturized, wearable, pump system that safely and effectively delivers drugs in various dosages over time to the inner ear in animal studies.[520] The device can also collect samples of inner ear fluid, which will help scientists with drug development and treatment. Because it can target inner ear fluid precisely, the device will serve as a useful tool for investigating the molecular mechanisms associated with inner ear diseases and for testing new treatments for hearing and balance problems.

NIDCD is also supporting a clinical trial that uses an auditory brainstem implant (ABI) in children who were born without an auditory nerve. An ABI, like a cochlear implant, consists of a microphone and transmitter worn on the side of the head. The transmitter converts sounds from the outside world into electrical signals. Those signals are transmitted to an internal receiver made up of electrodes that is implanted on the brainstem (unlike a cochlear implant, which stimulates the auditory nerve). The auditory neurons in the brain are stimulated directly, completely bypassing the inner ear. If the ABI is effective, physicians will have a viable treatment option for individuals born without an auditory nerve or with a disorder of the auditory nerve.[521]

Technology can also be used to improve the quality of life of people living with essential tremor disorder and PD. Through SBIR grants, NINDS supported the development of the adaptive technology that led to the Liftware spoon. This electronic spoon counteracts the movements caused by tremors, reduces shaking, and makes it easier to eat.[522] In 2014, Liftware Labs was acquired by Google.

For families with children who require cleft lip and/or palate treatment, NIDCR-funded investigators looked at whether the nasoalveolar molding procedure could improve outcomes when paired with the traditional treatment approach. Nasoalveolar molding is a treatment that is used to expand tissues

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[518] Mesulam M, et al. *Brain* 2015;138(Pt 8):2423-37. PMID: 26112340.
[519] Mirman D, et al. *Nat Commun* 2015;6:6762. PMID: 25879574.
[520] Tandon V, et al. *Biomed Microdevices* 2015;17(2):37. PMID: 25686902.
[521] https://clinicaltrials.gov/ct2/show/NCT02310399?term=auditory+brainstem+implant&rank=3.
[522] https://sbir.nih.gov/statistics/success-stories/lift-labs.

before surgery and improve the final results of surgical repair. This extra treatment places an additional burden on caregivers because it involves an appliance that requires daily adjustments. However, caregivers of children who received nasoalveolar molding plus traditional care reported less anxiety and better coping than caregivers of children who received traditional care only.[523] Ongoing research will examine how best to care for children with facial anomalies and the impact of specific interventions on caregivers.

Measuring disability is necessary for both treatment and support. The amount of work disability benefits that individuals receive from the Social Security Administration (SSA) is based on symptoms, medical evidence, and, to some extent, function. Current methods of disability assessment have limited precision and high costs, and they can impose patient burdens. Researchers at the NIH CC developed a novel disability assessment measure that uses large banks of questions addressing the full range of functioning in an area of interest and tailors questions to test takers based on their prior responses.[524] This assessment measure is more accurate and cost-effective than current assessment tools, making it suitable for widespread testing by SSA to assess physical and behavioral health function related to work disability.

[523] Sischo L, et al. *Cleft Palate Craniofac J* 2015;52(6):640-50. PMID: 25225840.
[524] Meterko M, et al. *Arch Phys Med Rehabil* 2015;96(6):1028-35. PMID: 25528263.

Chronic Diseases and Organ Systems

Defined as any condition lasting more than one 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. As of 2012, 117 million American adults—about half the U.S. population—had at least one chronic disease. There are many different categories of chronic disease. Some are fatal; in 2010, seven of the top 10 causes of death in the U.S. involved chronic diseases.[525] Others are debilitating; 12 percent of Americans are disabled or have had their activities limited due to chronic diseases.[526]

There are a multitude of contributors 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. Further, age plays a factor in the development and worsening of chronic conditions such as hearing loss, chronic kidney disease, vision loss, and osteoarthritis; genetics, which can cause chronic diseases at from birth (e.g., sickle cell anemia, hemophilia) and throughout development (e.g., asthma, allergies), also play a role.

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. 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 over 85 percent of the disease burden in high-income nations.[527]

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 where NIH is conducting critical research.

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 24 million Americans, including more than 6 million children age 18 and under.[528] Asthma is the leading cause of missed school days for children, a driver of preventable hospitalizations,

[525] https://www.cdc.gov/chronicdisease/overview/index.htm.
[526] Adams PF, et al. *Vital Health Stat* 2013;10(259):1-95. PMID: 24784762.
[527] Quam L, et al. *Lancet* 2006;368(9543):1221-3. PMID: 17027712.
[528] https://www.cdc.gov/asthma/most_recent_data.htm.

and emergency room visits. NIH supports targeted research aimed at improving our understanding of asthma, its causes, and how asthma can be prevented and treated in children and adults.

Understanding Prevalence, Risk Factors, and Underlying Biology

Women with asthma who become pregnant may face challenges in keeping their asthma under control. For a woman with asthma, the response of her immune system to pregnancy may be especially important to the health of both mother and child. NICHD's Breathe-Wellbeing, Environment, Lifestyle and Lung function (B-WELL-Mom) study aims to understand the impacts of asthma control on maternal immune regulatory processes throughout pregnancy and postpartum, as well as possible contributions of external factors, including air pollution and diet, to how well asthma is under control.[529]

During early life, recurrent wheezing and sensitivity to common allergens are risk factors for development of asthma. NIAID-funded scientists followed children at high risk of developing asthma in inner-city settings from birth to age 3 to evaluate whether exposure to certain bacteria and common allergens influenced whether the children developed asthma or allergies. The findings showed that inner-city children who had early-life exposure to high bacterial diversity and allergen levels were less likely to develop allergies and asthma.[530]

Other NIAID-supported researchers demonstrated how environmental exposures may protect against airway allergens and asthma. The study suggests that exposure to dust from homes with dogs may alter the immune response to allergens and other asthma triggers by affecting the composition of the gut microbiome, the community of microbes that naturally colonize the digestive tract. The findings showed that dust collected from homes with dogs contains a wider range of bacteria types than dust gathered from homes without dogs. Additionally, animal studies prompted by the observation that children from homes with dogs were less likely to develop allergies showed that mice exposed to dog-associated dust had fewer of the cells and immune-modulating chemicals involved in allergic responses.[531,532]

NIEHS grantees conducted research indicating that decreased air pollution levels over the past several decades in southern California was associated with improvements in respiratory health among children. Investigators from the Children's Health Study measured lung function annually in 2,120 children from three separate cohorts corresponding to three separate calendar periods. The researchers found that improvements in air quality were associated with significant improvements in lung-function development in both boys and girls and in children with and without asthma. [533,534]

Some children and adults with asthma experience worsening symptoms, particularly in the fall, despite treatment with doses of inhaled corticosteroids and other drugs that reduce impairment. These

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[529] https://www.nichd.nih.gov/newsroom/resources/spotlight/042415-DIPHR-report.
[530] Lynch SV, et al. *J Allergy Clin Immunol* 2014;134(3):593-601. PMID: 24908147.
[531] Fujimura KE, et al. *Proc Natl Acad Sci* 2014;111(2):805-10. PMID: 24344318.
[532] https://www.niaid.nih.gov/news-events/dust-homes-dogs-may-protect-against-allergies-asthma.
[533] http://www.ncbi.nlm.nih.gov/pubmed/25738666.
[534] http://www.niaid.nih.gov/news/newsreleases/2014/Pages/URECA.aspx.

exacerbations lead to higher healthcare costs and greater morbidity. NIAID-funded researchers conducted studies that showed the drug omalizumab nearly eliminated seasonal increases in asthma attacks in cases of difficult-to-treat asthma not adequately managed under current NHLBI guidelines.[535]

Improving Treatment and Prevention

NIAID intramural scientists have shown that a major *Aspergillus fumigatus* allergen called Alp1 can promote airway hyper-responsiveness by setting off a chain of cell-signaling events that leads to tightening of the airways. Researchers detected high levels of Alp1 in the airway smooth muscle of people with asthma, particularly those sensitive to *A. fumigatus*. These results suggest that asthma-associated inflammation and damage to airway linings may help promote entry of such allergens into the smooth muscle of the airways, so drugs that intervene in this process potentially could help reduce asthma symptoms.[536,537,538]

In 2015, the NIEHS Clinical Research Unit began recruiting patients for the Natural History of Asthma with Longitudinal Environmental Sampling study (NHALES), which 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 five-year study will provide free treatment, medications, and compensation so participants can get their asthma under control.[539]

Effective asthma self-care behaviors are an important component of a successful asthma management plan for children and adolescents. To expand asthma self-care education beyond health offices and clinics, a team of nurse specialists and teachers developed a school- and community-based asthma health education and counseling program for elementary school students and their family caregivers. In a recent NINR-supported randomized clinical trial, researchers found that students who received the new program demonstrated improvement in episode management and risk reduction/prevention behaviors, compared with students who received a control program. These findings demonstrate that integrating an asthma education program into the regular school curriculum holds promise for improving asthma management among elementary school students.[540]

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 severe. In the U.S., allergies are the sixth

[535] Teach SJ, et al. *J Allergy Clin Immunol* 2015;136(6):1476-85. PMID: 26518090.
[536] Balenga NA, et al. *Nat Commun* 2015;6:6763. PMID 25865874.
[537] http://www.nature.com/ncomms/2015/150413/ncomms7763/full/ncomms7763.html.
[538] http://www.niaid.nih.gov/topics/asthma/research/Pages/FungalAllergenFeature.aspx.
[539] http://www.niehs.nih.gov/research/clinical/studies/nhales/index.cfm.
[540] Kintner EK, et al. *J Spec Pediatr Nurs* 2015;20(1):62-75. PMID: 25443867.

leading cause of chronic illness, costing an estimated $18 billion annually and affecting more than 50 million Americans.[541]

Understanding Risk Factors, Prevalence, and Underlying Biology

Hypereosinophilic syndrome (HES) refers to a rare group of conditions that are associated with persistent eosinophilia—an increase in the number of eosinophils, a type of white blood cell that fights disease. Signs and symptoms vary based on which parts of the body are affected. Although most patients with HES have clinical signs and symptoms that can be attributed to damage to tissue by eosinophils, some patients remain asymptomatic or have signs and symptoms that are not understood (hypereosinophilia of unknown significance [HEUS]). A NIAID team of intramural researchers identified and characterized individuals with HEUS of five or more years' duration. The scientists compared HEUS patients, untreated patients with HES, and healthy normal volunteers. The study demonstrated that a subset of patients with HES do not develop clinical symptoms of HES over a prolonged period of time (up to 31 years). HEUS participants were indistinguishable from patients with untreated symptomatic HES by various lab tests and demographics.[542]

Research at the NIAID IRP is focused on understanding the cellular and genetic mechanisms responsible for allergic diseases, including food allergies. A better understanding of these mechanisms provides a basis for developing immunological therapies for food allergies. Ongoing NIAID IRP clinical trials include evaluation and long-term follow-up of patients with allergic and inflammatory disorders, and natural history and genetics of food allergy and related conditions, which is a new protocol for 2015.[543,544]

In the first study to use a genome-wide screening approach in patients with a well-defined food allergy, NIAID-funded research found that changes in a small region of chromosome 6 are risk factors for peanut allergy in U.S. children of European descent. The genetic risk area is located among two tightly linked genes that regulate the presentation of allergens and microbial products to the immune system.[545]

In another NIAID-funded study looking at genetics, researchers identified genetic markers associated with eosinophilic esophagitis (EoE), an inflammatory disease characterized by high levels of eosinophils in the esophagus. The findings suggest that several genes are involved in the development of EoE, which can cause difficulty eating and is often associated with food allergies. The findings may help explain why the disease specifically affects the esophagus.[546,547]

NIAID intramural scientists are also following a cohort of more than 350 patients with a variety of eosinophilic disorders. Clinical samples are collected to examine the role of eosinophils in the various disorders. NIAID researchers work with several ICs, including a collaboration with NIDDK to characterize

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[541] https://www.cdc.gov/healthcommunication/toolstemplates/entertainmented/tips/allergies.html.
[542] Chen YY, et al. *J Allergy Clin Immunol* 2014;133(4):1195-202. PMID 23987798.
[543] https://clinicaltrials.gov/ct2/show/NCT00557895.
[544] https://clinicaltrials.gov/ct2/show/NCT02504853.
[545] Hong X, et al. *Nat Commun* 2015;6:6304. PMID: 25710614.
[546] Kottyan LC, et al. *Nat Genet* 2014;46(8):895-900. PMID: 25017104.
[547] https://www.niaid.nih.gov/news-events/scientists-deepen-genetic-understanding-eosinophilic-esophagitis.

immune cells in patients with eosinophilic gastrointestinal disorders, an NCI partnership to develop biomarkers for hypereosinophilic disorders, an NHLBI collaboration to evaluate diagnostic imaging for cardiac pathology in eosinophilic disorders, and collaborative work with NIAMS to study biomarkers and novel therapies.

Additionally, research done by NIAID IRP scientists has characterized the contribution of estrogen to intensified anaphylactic responses in female mice. Anaphylaxis, a rapidly progressing, life-threatening allergic reaction, is more common in adult women than in adult men. These findings provide additional insights into risk factors and possible implications for clinical management of anaphylaxis.[548,549]

Other NIAID intramural researchers have identified a new genetic syndrome characterized by health problems such as severe allergy, immune deficiency, autoimmunity, and motor and neurocognitive impairment. The researchers observed that the syndrome's diverse symptoms are the result of mutations in a single gene, hypomorphic phosphoglucomutase 3 (*PGM3*). Impaired *PGM3* function was demonstrated by decreased enzyme activity and decreased protein glycosylation in patients' cells. These results define a new congenital disorder of glycosylation and suggest that other, less severe defects in glycosylation may play a role in more common allergic and immunologic diseases, opening potential new avenues for developing treatments.[550,551]

Improving Treatment and Prevention

Until recently there were no efficacious treatments for eosinophilic disorders, the type of inflammatory disorder discussed in the section above. In 2014, however, NIAID intramural scientists identified EMR1 (eosinophil surface receptor epidermal growth factor–like module containing mucin-like hormone receptor 1) as a potential therapeutic target.[552] [553]

NIAID-supported researchers designed a study called Learning Early About Peanut Allergy (LEAP), based on observations that Israeli children have lower rates of peanut allergy than Jewish children of similar ancestry residing in the U.K. do. Unlike children in the U.K., Israeli children begin consuming peanut-containing foods early in life. The study tested the hypothesis that the very low rates of peanut allergy in Israeli children were a result of high levels of peanut consumption beginning in infancy. This clinical trial found that introducing peanut products into the diets of infants at high risk of developing peanut allergy was safe and led to an 81 percent reduction in the subsequent development of the allergy.[554,555]

NIAID clinical researchers are also conducting a study of predictors of steroid responsiveness in HES characterized by a persistent elevation in eosinophil levels, as well as therapeutic trials of

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[548] Hox V, et al. *J Allergy Clin Immunol* 2015;135(3):729-36. PMID 25553642.
[549] https://www.niaid.nih.gov/news-events/estrogen-worsens-allergic-reactions-mice.
[550] Zhang Y, et al. *J Allergy Clin Immunol* 2014;133(5):1400-9. PMID 24589341.
[551] http://www.niaid.nih.gov/news/newsreleases/2014/Pages/GeneticSyndrome.aspx.
[552] Legrand F, et al. *J Allergy Clin Immunol* 2014;133(5):1439-47: PMID 24530099.
[553] http://www.niaid.nih.gov/topics/eosinophilicdisorders/Pages/default.aspx.
[554] Du Toit G, et al. *N Engl J Med* 2015;372(9):803-13. PMID: 25705822.
[555] http://www.niaid.nih.gov/news/newsreleases/2015/Pages/LEAP.aspx.

immunomodulatory agents, monoclonal antibodies, and tyrosine kinase inhibitors targeting eosinophils. Many of these studies are conducted in collaboration with the private sector and extramural researchers. The goals of these efforts are to improve treatment approaches, limit side effects, and develop new tools to speed diagnosis of eosinophil-associated disorders.[556]

An NIAID-supported clinical trial showed that high doses of the corticosteroid fluticasone propionate safely and effectively induce remission in many people with EoE. However, some trial participants did not respond to fluticasone even after six months of high-dose treatments, providing evidence that certain people with EoE are steroid-resistant. By analyzing gene expression—the degree to which certain genes are turned on or off—in esophageal tissues, scientists identified a cluster of genes that may help predict steroid responsiveness.[557,558]

Dust mites are a common allergen that can exacerbate symptoms of asthma and induce allergic responses. NIEHS scientists published the first study to demonstrate that the use of an in-home test kit can lead to a reduction in dust mite allergen levels in the home. The use of these kits may help people employ strategies to reduce the prevalence of those allergens.[559]

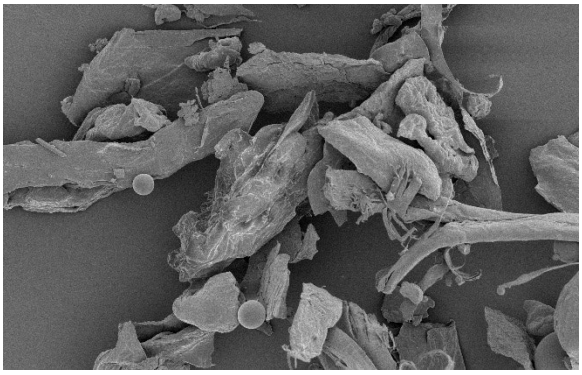

Figure 29. House dust under high magnification. Credit: NIAID.

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 sickle cell disease and Cooley's anemia. Patients with chronic anemias can experience

[556] https://clinicaltrials.gov/ct2/show/NCT01524536.
[557] Butz BK, et al. *Gastroenterology* 2014;147(2):324-33. PMID: 24768678.
[558] https://www.niaid.nih.gov/news-events/high-dose-fluticasone-effective-against-eosinophilic-esophagitis.
[559] Winn AK, et al. *J Asthma* 2016;53(2):133-8. PMID:26308287.

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.

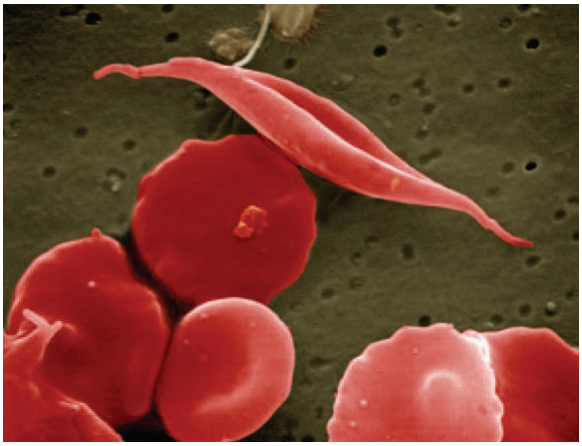

Figure 30. Scanning electron microscopy image revealing some of the structural morphology displayed by red blood cells in a patient with sickle cell disease. Credit: NIH.

Hundreds of thousands of Americans suffer from one or more types of blood diseases. For example, in 2013 alone there were more than 145,000 emergency department visits for anemia.[560] NIH's research into chronic blood disease leads to better understanding, treatment, and prevention of these disorders.

Understanding Prevalence, Risk Factors, and Underlying Biology

While it has long been known that bone marrow stromal cells are responsible for the support of hematopoiesis, or blood cell formation, it has only recently been recognized that these cells may also contribute to blood diseases and disorders. NIDCR intramural researchers discovered that bone marrow stromal cells from individuals with short telomeres (protective structures at the ends of each chromosome) were defective and unable to support hematopoiesis. Because of hematopoietic deficiencies, these individuals have major problems with their bone marrow. Further research on telomeres in bone marrow stromal cells could result in new approaches to treat bone marrow failure.[561]

In a study supported by NHLBI and NIDDK, researchers demonstrated how blood stem cells introduced into the tails of zebrafish adhere inside of blood vessels and then move to the outside of the vessel wall, filling what are called "niches." Further understanding of this process and the development of tools to observe it may help advance stem cell therapies in the future.[562]

A recent study identified a new protein hormone, erythroferrone, that comes from bone marrow to regulate hepcidin, which in turn regulates iron absorption in the intestine. Erythroferrone was

[560] https://www.cdc.gov/nchs/fastats/anemia.htm.
[561] Balakumaran A, et al. *Blood* 2015;125(5):793-802. PMID: 25499762.
[562] Tamplin OJ, et al. *Cell* 2015;160(1-2):241-52. PMID 25594182.

subsequently shown to contribute to recovery from anemia of inflammation, a type of anemia commonly associated with chronic, or long-term, illnesses or infections.[563,564]

X-linked sideroblastic anemia is an inherited disorder that prevents developing red blood cells from making enough hemoglobin—the protein that carries oxygen in the blood. A NIDDK-funded study found that approximately two-thirds of X-linked sideroblastic anemia cases are due to mutations in the *ALAS2* gene. The mutations result in a change in an enzyme called erythroid ALA-synthase, which plays a role in heme (a component of the hemoglobin protein).[565]

Improving Treatment and Prevention

SCD is an inherited blood disorder that affects millions of people worldwide and approximately 100,000 people in the U.S., including 1 in every 365 African Americans born.[566] In 2014, the drug candidate Aes-103, developed by researchers at NCATS, NHLBI, and AesRx, LLC, was the first to target the defect underlying SCD. AesRx obtained approval from FDA to conduct Phase I and II trials. The trials' success of led Baxter International's BioScience to acquire AesRx and to continue to develop Aes-103 for approval and commercialization.[567]

NHLBI-funded researchers have developed a method to target and correct the SCD gene mutation in patient-specific induced pluripotent stem cells (iPSCs)—cells taken from patients' blood or skin and genetically reprogrammed to an embryonic stem cell–like state. The researchers were able to correct the SCD mutation in patient-derived iPSCs by using the CRISPR/Cas9 system, which can cut DNA at precise locations and insert specific DNA sequences. These gene-corrected stem cells could have a number of applications in research and therapy, including serving as cells for transplantation in patients with SCD.[568]

Another set of NHLBI-supported researchers investigating SCD were able to demonstrate that zinc-finger nucleases, a tool for gene editing, can correct the hemoglobin mutation responsible for SCD. In one experiment, the researchers were able to correct the mutation in bone marrow cells from patients with SCD, and the corrected cells were able to produce normal hemoglobin in vitro.[569]

Another NHLBI-supported study showed that the drug hydroxyurea may be a viable substitute for regular blood transfusions in lowering the risk of stroke in children with SCD. Although they are the standard treatment for reducing stroke risk in these patients, blood transfusions carry a risk of iron overload, which can be toxic to the liver and heart. The study found that the drug hydroxyurea is no worse than regular blood transfusions at lowering transcranial Doppler (TCD) velocity—a measure of

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[563] Kautz L, et al. *Nat Genet* 2014;46(7):678-84. PMID: 24880340.
[564] Kautz L, et al. *Blood* 2014;124(16):2569-74. PMID: 25193872.
[565] Campagna DR, et al. *Am J Hematol* 2014;89(3):315-9. PMID: 24166784.
[566] https://www.cdc.gov/ncbddd/sicklecell/data.html.
[567] https://www.nih.gov/news-events/news-releases/first-drug-candidate-nih-program-acquired-biopharmaceutical-company.
[568] Huang X, et al. *Stem Cells* 2015; 33(5): 1470-79. PMID: 25702619.
[569] Hoban MD, et al. *Blood* 2015; 125(17):2597-604. PMID: 25733580.

blood flow in the brain—in children with SCD. High TCD velocities are associated with an increased risk for stroke.[570]

Building on decades of NIH-sponsored basic research, a private company recently tested a therapeutic agent designed to treat the vaso-occlusive crises (VOCs) that are a common painful complication of SCD and often require hospitalization. The new agent was designed to block circulating blood cells from adhering (sticking) to damaged blood vessel walls, which can be a trigger for crisis. When used in combination with intravenous opioids, the standard treatment for VOCs, the new treatment ended crises more quickly and reduced the amount of intravenous opioids given by 83 percent. Reducing opioid use to treat crises is an important goal, because opioids can cause multiple complications.[571]

Cardiovascular Diseases

Cardiovascular disease (CVD) is a broad term used to encompass many conditions, including heart diseases such as coronary heart disease, cardiomyopathy, heart failure, heart valve disease, sudden cardiac arrest, and congenital heart defects, as well as cerebrovascular disease (including stroke) and other disorders and conditions of the blood vessels, such as peripheral arterial disease and deep vein thrombosis. Heart disease is the single largest cause of death among U.S. men and women. Around one-quarter of deaths annually—about 610,000 per year—are caused by heart disease, and in 2009 half of all U.S. deaths were from heart disease and related conditions.[572]

Understanding Prevalence, Risk Factors, and Underlying Biology

NIH's research efforts involve discovering the basic mechanisms of CVD, as well as seeking to understand risk factors for developing CVD. For example, NIEHS-supported researchers evaluated more than 300,000 people ages 40–80 who were participating in Life Line vascular screening tests who had not previously had a procedure for carotid artery stenosis (CAS). Residents had a wide range of PM 2.5—particulate matter in the atmosphere that has a diameter less than 2.5 micrometers—exposure associated with CAS, an important risk factor for cerebrovascular disease and stroke. The investigators speculate that the findings for CAS may represent a pathway through which PM 2.5 exposure increases cardiovascular risk.[573]

Cholesterol-lowering drugs known as statins are commonly prescribed for people who have or are at risk for CVD. Because statins can cause muscle pain and other side effects, NIH-funded researchers are continuing to study the role of cholesterol in CVD to develop more effective medications. One area of research focuses on HDL (high-density lipoprotein) cholesterol, which is sometimes called "good" cholesterol because higher levels of it are associated with lower risks of coronary heart disease. HDL cholesterol partners with a protein called apoA1 to transport low-density lipoprotein (LDL, or "bad")

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[570] http://www.nhlbi.nih.gov/news/press-releases/2014/nih-ends-transcranial-doppler-tcd-transfusions-changing-hydroxyurea-twitch.
[571] Telen MJ, et al. *Blood* 2015;125(17):2656-64. PMID: 25733584.
[572] https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_disease.htm.
[573] Girirajan S, et al. *Hum Mol Genet* 2013;22(14):2870-80. PMID: 23535821.

cholesterol from arteries. But this transport system can break down, contributing to plaque buildup and coronary artery disease. NHLBI-funded investigators identified a chemical change in apoA1 that weakens the protein's ability to clean up LDL cholesterol. This research provides important insights into why HDL cholesterol is not always good, and findings could lead to the development of a blood test to better diagnose coronary artery disease.

Other NHLBI-supported researchers investigating cholesterol and other fats, called triglycerides, have found that loss-of-function mutations in a gene called *APOC3* are associated with lower triglyceride levels. This research suggests that inhibiting the APOC3 protein or expression of the *APOC3* gene may be an effective strategy for lowering the risk of heart disease.[574]

Although higher HDL cholesterol levels are associated with a lower risk of coronary heart disease, drugs that raise HDL cholesterol are not effective for treating coronary heart disease. In an NHLBI-funded study, researchers measured cholesterol efflux capacity (cleanup of cholesterol from artery walls) in 1,745 patients with incident coronary heart disease and in 1,749 control participants free of any cardiovascular disorders. The researchers found that cholesterol efflux was significantly higher in people with incident coronary heart disease, even after adjustment for age, sex, smoking status, and HDL levels. Thus, to treat heart disease, enhancing cholesterol efflux might be a better alternative than boosting HDL cholesterol levels.[575]

Related to the regeneration of heart tissues, NHLBI-funded researchers have identified a molecular mechanism within zebrafish for regenerating the heart that is present but silent in adult mammals. The researchers have also found a way to activate the molecular pathway in cultured human heart cells and in adult mice, where the experimental activation improved function in damaged hearts. Researchers will explore leveraging these mechanisms to develop methods of regenerating human heart tissue.[576]

Hypertension, or high blood pressure, is a leading cause of death and disability in the U.S. and worldwide. More than 60 percent of people over age 65 have hypertension, and it is on the increase. In an NHLBI-funded study, researchers discovered a mechanism that links hypertension to inflammation inside blood vessels. They found that in mice and humans with hypertension, highly reactive chemicals called isoketals appear to trigger harmful changes in immune cells that lead to inflammation. In mice, chemicals that neutralize isoketals helped prevent hypertension. The researchers are developing this strategy into a product through the NHLBI Vascular Interventions/Innovations and Therapeutic Advances (VITA) program.[577]

Preeclampsia is a condition that affects up to 10 percent of pregnant women worldwide; it causes hypertension and can lead to seizures, stroke, organ damage, and even death. The causes are largely unknown, and the only cure is delivery of the child.[578] NHLBI-supported researchers have found

[574] NHLBI TG and HDL Working Group, et al. *N Engl J Med* 2014;371(1):22-31. PMID: 24941081.
[575] Saleheen D, et al. *Lancet Diabetes Endocrinol* 2015;3(7):507-13. PMID: 26025389.
[576] Aguirre A, et al. *Cell Stem Cell* 2014;15(5):589-604. PMID: 25517466.
[577] Kirabo A, et al. *J Clin Invest* 2014;124(10):4642-56. PMID: 25244096.
[578] https://www.nichd.nih.gov/health/topics/preeclampsia.

evidence that preeclampsia is caused by abnormal protein folding, similar to the mechanism that causes protein clumps in many diseases, including Alzheimer's. The researchers also found that a urine test to measure protein misfolding may help predict who will develop preeclampsia. These results could enable early diagnosis of preeclampsia, as well as treatment approaches that target protein misfolding.[579]

Certain conditions increase the risk for CVD. An NHLBI-supported study found that the buildup of soft plaque in arteries that nourish the heart is more common and extensive in HIV-positive men than in HIV-negative men, independent of other heart disease risk factors. The findings add to the evidence that HIV-positive men are at greater risk for heart disease than HIV-negative men of the same age.[580]

NIAMS researchers have identified mechanisms leading to CVD in childhood-onset systemic lupus erythematosus (SLE). Compared to those without lupus, SLE patients have a significantly greater risk of developing premature atherosclerotic CVD, premature coronary heart disease (CHD) or atherosclerosis, stroke, and other cardiovascular-related conditions. Childhood-onset SLE (cSLE) patients carry a longer burden of disease due to their younger age of onset, and subclinical atherosclerosis as a result of endothelial damage is commonly reported. NIAMS intramural researchers have identified an important role for type I interferons (IFNs) in the development in cSLE and adult-onset SLE (aSLE). The type I IFNs promote significant impairment of endothelial progenitor cells (EPCs) and prevent their development into mature endothelial cells (ECs), leading to decreased vascular function. Researchers identified decreased numbers and function of circulating EPCs in cSLE patients, as in other pediatric autoimmune diseases. The results suggest that cSLE, like aSLE, is characterized by impairment and decreased function of EPCs, likely initiated by type I IFNs.[581]

Researchers from the NHLBI Pediatric Cardiac Genomics Consortium identified a link between genes associated with the development of CHD and certain neurodevelopmental abnormalities in children. Using exome sequencing, investigators found that two percent of children with moderate to severe CHD had de novo gene mutations (i.e., mutations not found in their parents). Among children who had both CHD and neurodevelopmental abnormalities, 20 percent had these gene mutations. If confirmed, these findings could lead to genetic tests to help identify patients with CHD at high risk for neurodevelopmental abnormalities and target them for early intervention.[582]

Improving Treatment and Prevention

The NHLBI Programs of Excellence in Nanotechnology (PEN) supported a study in which researchers created nanoparticles that could deliver statins directly to artery-clogging plaques, where the statins reduced inflammation and inhibited plaque progression. The researchers developed these statin-loaded nanoparticles to overcome the practical limits of oral statins: At normal doses, oral statins never reach plaques, and at higher doses, they have toxic effects elsewhere. To ensure that the nanoparticles would be targeted to plaques, the researchers fashioned the nanoparticles out of reconstituted high-density

[579] Buhimschi IA, et al. *Sci Transl Med* 2014;6(245):245ra92. PMID: 25031267.
[580] Post W, et al. *Ann Intern Med*. 2014;160(7):458–467. PMID: 4143766
[581] Mohan S, et al. *Arthritis Rheumatol*. 2015;67(8):2257-62. PMID: 25891295
[582] Homsy J, et al. *Science* 2015;350(6265):1262-6. PMID: 26785492.

lipoprotein (which naturally accumulates as plaques). One potential clinical use of the statin-loaded nanoparticles would be to suppress plaque inflammation following a heart attack, when patients are at risk for further plaque ruptures and heart attacks.[583]

Scar tissue formation inside arteries is a major problem that limits the benefits of coronary bypass surgeries. NHLBI-supported researchers have found that in mice, molecules called resolvins, so named because they help resolve inflammation, can help heal blood vessels after surgery. In the VITA program, the same researchers are developing these anti-inflammatory compounds into prototype drugs to reduce vascular scarring and improve surgical outcomes.[584]

In 2014, NLM began funding a project to enhance the biocompatibility and effective life of synthetic replacements for cardiac and vascular structures. The method is based on evolving technologies that generate materials for reducing immunogenicity, thrombosis, and infection at critical tissue–device interfaces. Progress has been made in developing a protocol to decellularize heart tissues and to develop a strategy to 3D-print different designs incorporating biomatrices. If successful, this project would be transformative for replacement cardiovascular therapy.[585]

Although the anticoagulant warfarin is an effective therapy for reducing the risk of heart attacks and strokes, determining the best dose of this blood thinner for each patient can be challenging. Some people need a high dose, but others risk internal bleeding from relatively low doses. Small studies have suggested that genotype testing could be used to customize warfarin dosing. The Clarification of Optimal Anticoagulation through Genetics (COAG) study was an NHLBI-sponsored, multicenter trial that compared genotype-guided dosing to clinical dosing alone (e.g., factoring in age, race, and smoking; measuring the rate of blood clotting). Overall, genotype-guided dosing was no better than clinical dosing at bringing patients to a safe, effective dose range of warfarin. The study emphasizes the importance of performing large controlled trials to evaluate pharmacogenetics approaches, particularly for complex regimens such as warfarin dosing.[586]

NIH-supported investigators recently found that, in a group of adults age 50 and older with high blood pressure, intensive management of high blood pressure below a commonly recommended blood pressure target significantly reduces rates of cardiovascular disease and lowers risk of death. These findings come from the landmark Systolic Blood Pressure Intervention Trial (SPRINT), which is supported by NHLBI, NIA, NINDS, and NIDDK. The intervention in this trial, which carefully adjusts the amount or type of blood pressure medication participants receive to achieve a target systolic pressure of 120 millimeters of mercury (mmHg), reduced rates of cardiovascular events, such as heart attack, heart failure, and stroke, by almost one-third and the risk of death by almost one-quarter, compared with the target systolic pressure of 140 mmHg. The results of this trial provide crucial evidence about optimal

[583] Duivenvoorden R, et al. *Nat Commun* 2014;5:3065. PMID: 24445279.
[584] Akagi D, et al. *FASEB J*. 2015;29(6):2504-13. PMID: 25777995.
[585] https://projectreporter.nih.gov/project_info_description.cfm?aid=8930186&icde=34668854.
[586] Kimmel SE, et al. *N Engl J Med* 2013;369(24):2283-93. PMID: 24251361.

blood pressure control targets and will influence clinical- and population-level stroke prevention efforts.[587,588]

Fast and accurate identification of CVD symptoms helps saves lives. To better characterize the many adverse symptoms of heart failure across different populations, NINR-funded scientists compared data describing the symptoms of 720 heart failure patients across China, Taiwan, the Netherlands, Sweden, and the U.S. They identified two groups of associated symptoms, or symptom clusters, that were consistent across all patients: (1) a physical capacity symptom cluster that included dyspnea (shortness of breath), difficulty walking or climbing, and fatigue; and (2) an emotional/cognitive symptom cluster that included worrying, feeling depressed, and cognitive problems. These findings, which indicate that symptoms of heart failure are consistent across cultures, are important for improving symptom recognition and acting early to avoid adverse outcomes.[589]

In another NINR-funded study, a nurse-delivered chronic heart failure intervention that consisted of identification of medication goals, medication-symptom association, and a symptom response plan was tested in a proof-of-concept study among patients at high risk for poor medication adherence. The patients in the intervention group in this study were almost four times as likely as the control group to be adherent to their medications a year after the intervention.[590]

NINR researchers also discovered that normal prehospital electrocardiographies (ECGs) were linked to long-term survival in emergency room (ER) patients with symptoms of acute coronary syndrome. Normal prehospital electrocardiogram findings in individuals with chest pain and/or other anginal symptoms are associated with fewer adverse health outcomes, shorter hospital stays, and better long-term mortality rates than in people with abnormal ECGs.[591]

Following a recommendation from the 2012 NINDS Stroke Research Priorities Meeting, NINDS established the national Stroke Trials Network to more efficiently develop, promote, and conduct high-quality, multisite clinical trials to test promising interventions in stroke prevention, treatment, and recovery. Through prioritization of research questions, harmonization and sharing of data collected in trials, and research training opportunities, the interdisciplinary network will provide expertise and infrastructure for NIH-sponsored stroke clinical trials and build research capabilities that match scientific opportunities across the spectrum of stroke research. During FY 2014 and FY 2015, the network became operational and initiated the first trials. It is currently conducting trials in areas such as stroke prevention, treatment for ischemic and hemorrhagic stroke, and recovery.[592]

NINDS continues to develop and manage the Institute's groundbreaking public education campaign, *Know Stroke. Know the Signs. Act in Time*. The campaign was designed to help increase knowledge and

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[587] SPRINT Research Group, et al. *N Engl J Med*. 201;373(22):2103-16. PMID: 26551272.
[588] https://www.nih.gov/news-events/news-releases/landmark-nih-study-shows-intensive-blood-pressure-management-may-save-lives.
[589] Moser DK, et al. *Int J Nurs Stud* 2014 Oct;51(10):1366-72.PMID: 24636665.
[590] Granger BB, et al. *Am Heart J* 2015;169(4):539-48. PMID: 25819861.
[591] Zègre-Hemsey JK, et al. *J Electrocardiol* 2015;48(4):520-6. PMID: 25683824.
[592] https://www.nihstrokenet.org/.

awareness about the early warning signs and symptoms of stroke and to drive behavior change, especially in at-risk communities. It includes outreach to consumers and health care professionals via mass media, social media, grassroots partnerships, and community education. The foundation for this initiative is community engagement through "train the trainer" programs in major urban areas across the U.S.; the programs use NINDS materials to educate local high-risk audiences, including African Americans, Hispanics, and people over age 50 and their family members, caregivers, and health care providers.[593]

NHLBI, along with NIAID, has launched a multicenter international clinical trial to test whether statins can reduce the risk of major adverse cardiovascular events, such as heart attacks, strokes, and heart disease, in people with HIV. Known as the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), the trial is the largest to date focused on preventing heart disease in people living with HIV.[594]

The NHLBI-funded Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study evaluated stenting to treat atherosclerosis and stenosis (narrowing) of arteries in the kidney. Stenting showed promise in older studies, and its use increased dramatically among Medicare beneficiaries in the late 1990s, but its benefits remain unclear. CORAL enrolled nearly 1,000 patents, with about half receiving medical therapy alone (e.g., anti-hypertensive drugs) and the other half receiving medical therapy plus stenting. The two groups did not differ in terms of deaths from cardiovascular or renal causes, heart attack, stroke, hospitalization for congestive heart failure, or other outcomes. The authors concluded that medical therapy without stenting is the preferred management strategy for most people with atherosclerotic renal-artery stenosis.[595]

In FY 2014, NHLBI's Pediatric Heart Network reported the latest results of a trial to compare two surgeries for congenital heart defects that are typically fatal in infancy. The Single Ventricle Reconstruction (SVR) trial randomized 549 patients with single ventricle cardiac anomalies to establish pulmonary blood flow with either a right ventricle-to-pulmonary artery shunt (RVPAS) or a modified Blalock-Taussig shunt (MBTS). At one year, transplant-free survival was better for the RVPAS than the MBTS. However, a follow-up study has found that at three years, transplant-free survival did not differ between the two groups. Continued follow-up of these patients is ongoing and will help to better characterize the relative benefits and risks of these two surgical procedures.[596]

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. Chronic fatigue syndrome is diagnosed 2–6

[593] https://stroke.nih.gov/.
[594] http://www.nhlbi.nih.gov/news/press-releases/2014/hiv-infected-men-at-increased-risk-for-heart-disease-large-study-finds.
[595] Cooper CJ, et al. *N Engl J Med* 2014;370(1):13-22. PMID: 24245566.
[596] Newburger JW, et al. *Circulation* 2014;129(20):2013-20. PMID: 24705119.

times more often in women than in men. The condition is difficult to diagnose because of multiple diagnostic criteria used by various practitioners as well as a by the lengthy timeframe for occurrence and recurrence of the symptoms. CDC indicates that for a patient to be diagnosed with chronic fatigue syndrome, symptoms must have persisted or recurred during six or more consecutive months of illness.[597] 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.

Understanding Prevalence, Risk Factors, and Underlying Biology

NIH has encouraged research on CFS through two parent funding opportunity announcements (FOAs) for R01 and R21 grants. NINDS, NIAID, and NINR together have funded seven R01s[598] and five R21s[599] on etiology, diagnosis, pathophysiology, and treatments. NINDS supports several projects on CFS, including studies examining gender difference in ME/CFS, exploring the differences in messenger-inhibiting RNA and protein expression to identify potential biomarkers and new targets for CFS treatments, utilizing gene sequencing technology with standardized exercise testing to examine exercise response, and studying the potential benefits of using oral rehydration to reduce orthostatic intolerance (experiencing symptoms while standing).

NIAID supports CFS research by funding projects with several different objectives. One project, a prospective study in college-aged adults to assess risk factors in developing ME/CFS following infectious mononucleosis, seeks to better understand the potential role of viral infections in the development of CFS. Another study, this time in mice, is testing the hypothesis that a new class of pathogen-associated molecular pattern proteins have novel immunoregulatory and neuroregulatory functions involved in CFS.

Other NIAID studies are identifying biomarkers of CFS. One study is using state-of-the-art methods for microbial surveillance and discovery to test the hypothesis that people with CFS and healthy controls have different bacterial, fungal, or viral microflora in the throat, lower gastrointestinal tract, and blood. A longitudinal study seeks to understand immune dysfunction that results from or predisposes people to herpes infection, as well as the dysfunction's potential relationship to ME/CFS.

Improving Treatment and Prevention

The NIH ODP coordinates the Pathways to Prevention (P2P) workshop program to identify prevention research gaps in selected scientific areas and to develop recommendations to move incomplete or underdeveloped fields of research forward through an unbiased, evidence-based assessment of a complex public health issue. In FY 2015, ODP hosted a workshop, "Advancing the Research on Myalgic

[597] https://www.cdc.gov/cfs/general/index.html.
[598] https://grants.nih.gov/grants/guide/pa-files/PAR-12-032.html.
[599] https://grants.nih.gov/grants/guide/pa-files/PAR-12-033.html.

Encephalomyelitis/Chronic Fatigue Syndrome." The recommendations from that event will inform future FOAs on CFS.[600]

Chronic Pain and Palliative Care

While acute pain is a normal sensation triggered in the nervous system to alert you to possible injury and the need to take care of yourself, chronic pain is different in that it persists for weeks, months, 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 medical care for those suffering serious illnesses, focusing on providing relief from the symptoms such as pain, nausea, constipation, and trouble sleeping.

Understanding Prevalence, Risk Factors, and Underlying Biology

NCCIH conducted an analysis of data from the 2012 National Health Interview Survey (NHIS) and found that most American adults have experienced some level of pain, from brief to more lasting (chronic) pain and from relatively minor to more severe pain. The analysis found that an estimated 25.3 million adults (11.2 percent of the population) experience chronic pain. Nearly 40 million adults (17.6 percent of the population) experience severe levels of pain. Those with severe pain are also likely to have worse health status.[601]

Children with intellectual or neurodevelopmental disabilities, such as cerebral palsy, may experience pain more frequently than their typically developing peers but may be nonverbal or may otherwise unable to tell their caregivers and clinicians that they are in pain. To investigate possible new methods of diagnosing pain, NICHD-funded researchers conducted a preliminary feasibility study to identify and compare a set of biomarkers in saliva in two small groups of children with cerebral palsy, one known to experience chronic pain and the other without such pain. Several types of molecules were found to differ in the saliva of the two groups, raising hope that further research will lead to a reliable, objective pain screening tool for use in children unable to communicate their pain.[602]

Another NICHD-supported study has offered useful insights into the poorly understood process by which normal, acute pain after an injury transitions into chronic pain for some people. An injury prompts the body to release natural opioid-like pain-relieving substances that act on the same brain and spinal cord pain receptors as morphine and other opioid drugs. Using mice with laboratory-induced foot injuries, scientists studied the behavior of spinal cord pain receptors and found that the receptors were activated for 21 days after the injury, even though injury-induced inflammation and sensitivity to pain resolved within 10 days. Blocking the receptor activity after 10 days post-injury caused the animals' pain

[600] https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs.
[601] Nahin RL. *J Pain* 2015;16(8):769-80. PMID: 26028573.
[602] Symons FJ, et al. *Pain Med* 2015;16(2):249-56. PMID 25234580.

sensitivity to return, thus indicating that continuous, post-injury activity of the receptors appeared to be the body's way of preventing acute pain from becoming chronic.[603]

The main focus of the Grand Challenge on Chronic Neuropathic Pain, an NIH Blueprint–supported program, is to study the transition from acute to chronic neuropathic pain and to gain an understanding of the biological mechanisms responsible for this transition, including the role of maladaptive neuroplasticity. In FY 2015, the Challenge funded 10 R01 grants and two supplements via two RFAs. Recent results supported by NINDS, NIDCR, and NIGMS have shown that after a peripheral nerve injury, TRPV1 ion channels exhibit hyperactivity in the spinal cord, maintained by serotonergic signals descending from the brain stem, suggesting a central nervous system malfunction in chronic pain.[604] Other results supported by NINDS and NIDCR from animal models and human studies of neuropathic pain suggest that the activity level in brain circuitry connections changes during the conversion from acute to chronic pain and involves several regions, including the cortex, striatum, and nucleus accumbens.[605]

Many chronic pain conditions are more prevalent in women than in men, and women and girls with these conditions tend to report more severe, frequent, and longer-lasting pain than their male counterparts. A study of possible explanations has revealed significant differences in how women and men experience pain. In experiments conducted in 48 healthy volunteers free of chronic pain conditions, researchers found significant differences between women and men both in their sensitivity to pain and in pain inhibition, even after the researchers controlled for influential factors such as sleep quality and depressive symptoms. Men were more tolerant of pain and showed more efficient pain conditioning than women. The results suggest that there are underlying biological differences between women and men in pathways involved in detection and response to potentially painful stimuli, possibly both explaining sex differences in prevalence and experience of chronic pain and pointing the way to future studies that could lead to improved and personalized pain treatment.[606]

NICHD-supported research with a large group of women who had undergone minimally invasive gynecologic surgery (laparoscopy or laparotomy) for diagnosis and/or therapy for diverse symptoms found that women diagnosed with endometriosis reported significantly higher chronic and cyclic pain than did women with other gynecological disorders (e.g., uterine fibroids, pelvic adhesions) or women without such pathology. Results also suggested that pelvic pain is common among women undergoing the procedure, even those for whom the surgery identified no gynecologic pathology. Investigators recommended further research on possible causes of pelvic pain in women seeking gynecologic care but without apparent gynecologic pathology. [607]

Although women are at greater risk for common forms of chronic pain, including orofacial pain, little is known about the role that sex and gender may play in pain processes. NIDCR-supported investigators

[603] Corder G, et al. *Science* 2013;341(6152):1394-9.PMID 24052307.
[604] Kim YS, et al. *Neuron* 2014;81(4):873-87. PMID: 24462040.
[605] Chang PC, et al. *Pain* 2014;155(6):1128-39. PMID: 24607959.
[606] Bulls HW, et al. *J Pain Res* 2015;8:311-20. PMID: 26170713.
[607] Schliep KC, et al. *Hum Reprod* 2015;30(10):2427-38. PMID: 26269529.

studied the interactions between immune cells and neurons in a mouse model of persistent neuropathic pain and found that different cell types relayed pain signals from the immune system to the nervous system in male and female mice. In female mice, pain signals were relayed by adaptive immune cells (T cells), while in male mice microglia, the immune cells of the brain and spinal cord, relayed those signals. Upon testosterone administration, pain relays in female mice switched to using the male-specific cells. One major implication of these findings is that distinct strategies targeting neuroimmune signaling might be required for the treatment of chronic pain in men versus women.[608]

NIDCR-supported researchers have also developed a clinically important and valid rodent model of two overlapping chronic pain conditions, temporomandibular disorder (TMD) and irritable bowel syndrome (IBS). A priming event in this model (i.e., muscle injury) leads to a heightened state of pain sensitivity that, in the presence of a stressor and fluctuating hormone levels, develops into a pain disorder with symptoms indicative of multiple conditions. Development of this model provides a significant resource for exploring the factors responsible for inducing overlapping pain conditions and an avenue for testing promising therapeutic approaches.[609]

NIDCR-supported Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) Phase II study continues to leverage the prospective cohort established in Phase I to further define the incidence and risk factors for orofacial pain conditions. In alignment with NIH's precision medicine efforts, as well as the Pain Consortium's efforts in overlapping pain conditions and diagnostics/prognostics, Phase II aims to identify clinically assessable factors that predict the risk of transition from acute to chronic TMD, risk factors for first-onset TMD and of co-morbid pain conditions, and genetic variants that influence risk of chronic TMD.[610]

A collaborative study involving NCCIH funding—this time with NIAMS and NIA—suggests that disruption of brain signals contributes to increased pain sensitivity, known as hyperalgesia, in patients with fibromyalgia. The investigators hypothesize that this altered brain processing might contribute to widespread pain and lack of response to opioid therapy in such patients.[611]

The interdisciplinary Specialized Center of Research (SCOR) on Sex and Gender Factors Affecting Women's Health was established through an ORWH program and is co-funded by NIDDK and ORWH. This SCOR is studying the interplay between gut and brain pathways in IBS and interstitial cystitis/bladder pain syndrome, focusing on sex differences in the development, clinical manifestation, and treatment response in these pain syndromes. One SCOR report suggests that in people of both sexes who who develop IBS, a history of early adverse life events (EALs) helps shape the resting state of a brain network that has been implicated in pain amplification. The report also notes that men with IBS experience EAL-related alterations in an additional brain network that is associated with fear perception,

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[608] Sorge RE, et al. *Nat Neurosci* 2015;18(8):1081-3. PMID: 26120961

[609] Traub RJ, et al. *J Pain* 2014;15(9):956-66. PMID: 24981128.

[610] http://www.nidcr.nih.gov/ScienceSpotlight/InterviewsbyTopic/TMJDisorders/OPPERA.htm?_ga=1.19832504.1454906391.1441662091.

[611] Loggia ML, et al. *Arthritis Rheumatol* 2014;66(1):203-12. PMID: 24449585.

motor function, and visual-motor learning. Another study uncovered sex differences in brain responses of women and men with IBS who were shown images of human faces expressing fear and anger; in contrast to prior findings with IBS-related stimuli, these non-IBS-related stimuli evoked greater responses in men with IBS than in women with IBS. These and similar studies underscore the importance of examining sex differences to potentially better target interventions for women and men with IBS.[612,613]

The NIDDK-led Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network includes multiple centers conducting innovative, collaborative studies of interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). These studies look beyond the bladder and prostate to find the causes of these conditions and the possible relationships between these conditions and other chronic pain disorders, such as IBS and fibromyalgia. In its first phase, the MAPP Research Network has supported several key discoveries, including:

- Uncovering potential biomarkers for IC/BPS in women[614]
- Visualizing multiple differences in the central nervous system between women and men with IC/BPS and CP/CPPS, respectively, and their healthy counterparts; these differences are now being pursued for their potential role(s) in symptom manifestation, persistence, and amelioration[615,616,617,618,619]
- Establishing the importance of symptom "flares" reported by patients both in assessing IC/BPS and in patient quality of life[620]

Emerging findings include new insights into the course of IC/BPS and CP/CPPS; differences between patients and healthy counterparts in microbes associated with the bladder; and different, potentially clinically relevant subgroups among people diagnosed with these conditions. In FY 2014, NIDDK, with co-sponsorship from ORWH, renewed the MAPP Research Network for a second 5-year phase to continue studies that could provide a foundation for effective clinical interventions for people with IC/BPS and CP/CPPS.[621]

Up to one-quarter of Americans experience low-back pain each year. For some people, that pain becomes chronic, a condition that costs the U.S. at least $100 billion per year. Current best practices for diagnosing and treating chronic low-back pain (cLBP) have yielded only limited success. In addition, consistency issues have made it difficult to compare, replicate, and reach consensus across results of cLBP studies. In 2012, NIH convened a Task Force on Research Standards for Chronic Low-Back Pain,

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[612] Gupta A, et al. *Psychosom Med* 2014;76(6):404-12. PMIDs: 25003944.
[613] Labus JS, et al. *Pain* 2013;154(10):2088-99. PMID: 23791896.
[614] Schrepf A, et al. *Brain Behav Immun* 2015;49:66-74. PMID: 25771510.
[615] Farmer MA, et al. *J Urol* 2015;194(1):118-26. PMIDs: 25711200.
[616] Martucci KT, et al. *Pain* 2015;156(9):1755-64. PMID: 26010458.
[617] Kutch JJ, et al. *Neuroimage Clin* 2015;8:493-502. PMID: 26106574.
[618] Kilpatrick LA, et al. *J Urol* 2014;192(3):947-55. PMID: 24681331.
[619] Kairys AE, et al. *J Urol* 2015;193(1):131-7. PMID: 25132239.
[620] Sutcliffe S, et al. *Int Urogynecol J* 2015;26(7):1047-60. PMID: 25792349.
[621] http://www.mappnetwork.org/.

comprising 16 invited experts from varied disciplines and from scientific and research institutions outside NIH. The NIH Pain Consortium's charge to this group included developing a set of standards to increase the consistency of future clinical research on cLBP. In April 2014, the task force began to release publications on its work, including a full report with recommendations on standards, an executive summary, journal articles, and a uniform minimal dataset. The recommendations, considered a dynamic document, are intended to help advance the field, resolve controversies, and ease the way in future cLBP research. The task force's report was published in four medical journals: *The Journal of Pain, Pain Medicine, The Spine Journal,* and *European Spine Journal*.[622,623]

Improving Treatment and Prevention

Research at Stanford University, funded in part by NCCIH, created an innovative way to produce opioid drugs from sugar by using genetically modified yeast. Using genes from a variety of plants, mammals, and microorganisms, researchers created yeast cells that can perform the entire process of using sugar to manufacture the opioids thebaine and hydrocodone l—a process that involves more than 20 separate steps. The new technique illustrates the potential value of genetically engineered yeast as a platform for producing many complex chemicals and materials.[624]

An estimated 1.7 million children in the U.S. experience chronic pain, but it is often difficult for clinicians to determine the best care for them. Treating chronic pain in adults is typically informed by patients' responses on pain screening questionnaires, but such tools have not been widely available for pediatric use. NICHD-supported researchers have now validated such a questionnaire in a large group of children ages 8 to 18 who sought care at a chronic pain clinic. This pediatric questionnaire was able to identify children with the highest risk of such poor outcomes as disability and emotional distress, important factors in care decisions.[625]

An ongoing NIDDK-sponsored program, the IBS Outcome Study, is a multicenter, placebo-controlled randomized clinical trial intended to determine whether self-administered cognitive behavioral therapy is as helpful as standard therapy with a therapist in reducing IBS symptoms and overall burden. One IBSOS study from 2014 showed that the fear of IBS symptoms had a major impact on reducing individuals' day-to-day quality of life, even more than the symptoms themselves did.[626] Another analysis from 2014 revealed that factors such as stress, depression, and anxiety were associated with a perception of being in worse health in people with IBS; surprisingly, as with the other analysis, the severity of IBS symptoms played a smaller role in participants' self-assessments of their overall health.[627] In 2015, a study showed that the self-reporting of symptoms by patients with IBS varied in accuracy

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[622] http://painconsortium.nih.gov/NIH_Pain_Programs/Task_Force/cLBP_RTF_FullReport.pdf.
[623] https://www.nih.gov/news-events/news-releases/chronic-low-back-pain-research-standards-announced-nih-task-force.
[624] Galanie S, et al. *Science* 2015;349(6252):1095-100. PMID: 26272907
[625] Simons LE, et al. *Pain* 2015;156(8):1511-8. PMID: 25906349
[626] Lackner JM, et al. *Am J Gastroenterol* 2014;109(11):1815-23. PMID: 25223577
[627] Lackner JM, et al. *Am J Gastroenterol* 2014;109(2):224-33. PMID: 24419481

depending on when the reporting took place and on whether it was at the group or individual level.[628] These studies suggest that greater awareness of and attention to the complex factors influencing individual experience of IBS may help health care providers in improving delivery and effectiveness of care, relationships with patients, and patient satisfaction and compliance with medical care.

ORWH funded an administrative supplement to investigate sexual dimorphism in the transition from acute to chronic pain. The investigators also sought to identify novel approaches for developing new classes of treatments for chronic pain. The work resulted in a 2016 *Nature* article that demonstrated sexual dimorphism in how much of a drug was required to induce hyperalgesic priming, an estrogen-dependent model of transition to chronic pain.[629,630]

In 2014, NCCIH, along with NIDA and VA, issued a funding initiative focused on nonpharmacological approaches to pain management in military personnel, veterans, and their families. Thirteen research projects totaling approximately $21.7 million over 5 years will explore nondrug approaches to managing pain and related health conditions such as PTSD, drug abuse, and sleep issues.

NIAMS has funded Physical Therapy as a First Option for Chronic Low Back Pain because of findings from Spinal Stenosis: The Spine Patient Outcomes Research Trial (SPORT), a study that has been comparing surgical and nonsurgical treatment for the three most common causes of severe, chronic low-back pain. SPORT has shown that patients who have surgery initially do better than people who have other, non-operative treatments, although people who choose to delay surgery are not doing any further damage as long as their pain is tolerable and not worsening. Recent SPORT results have shown that the differences between the people who had surgical or non-surgical treatments for spinal stenosis decrease with time, becoming nearly equivalent between five and eight years after surgery. Consistent with SPORT's findings, data from a group studying a specific physical therapy strategy also showed that postponing surgery in favor of a more conservative approach does not cause further harm. Moreover, when combined with the SPORT finding that the benefits of surgery fade over several years, the results strongly suggest that most people who have lumbar spinal stenosis should try a standardized physical therapy regimen before considering surgery.[631,632]

Led by NIDA, the NIH Pain Consortium,[633] established to enhance pain research and promote collaboration among researchers across the many NIH ICs that have programs and activities addressing pain, funded 11 Centers of Excellence for Pain Education (CoEPEs) in September 2015. The program is working to develop and distribute pain management curriculum resources for medical, dental, nursing, and pharmacy schools to advance the diagnosis and safe treatment of pain, while minimizing risks of

[628] Lackner JM, et al. *Neurogastroenterol Motil* 2014;26(12):1802-11. PMID: 25424582
[629] Ferrari LF, et al. *Sci Rep* 2016;6:31221. PMID: 27499186.
[630] https://projectreporter.nih.gov/project_info_description.cfm?aid=8976453&icde=34605266.
[631] Lurie JD, et al. *Spine (Phila Pa 1976)* 2015;40(2):63-76. PMID 25569524.
[632] Delitto A, et al. *Ann Intern Med* 2015;162(7):465-73. PMID: 25844995.
[633] https://painconsortium.nih.gov/.

addiction and diversion. The first curriculum resource resulted in an improvement in medical student exam scores. Each of the 11 CoEPEs is now developing a case-based module for review.[634]

Severe postoperative pain and persistent pain following root canal therapy (RCT) still occur despite improvements in care. In a prospective study conducted within the National Dental Practice-Based Research Network, the authors determined that nearly 20 percent of study patients reported severe postoperative pain one week following RCT, and 10 percent had persistent pain 6 months later. Pain intensity during the week before RCT significantly increased the risk of developing persistent pain, and optimism about the procedure reduced the risk. Considering these factors can help clinicians identify patients at risk for persistent pain and may suggest appropriate preventive interventions.[635]

The Palliative Care Research Cooperative (PCRC), which includes more than 20 member institutions across the nation, addresses national research priorities in palliative care and end of life by enhancing the quality and efficiency of research and educating clinicians and patients about best practices. The new award allows investigators from PCRC sites and others to propose studies that take advantage of PCRC's expertise, methodological resources, patient population, and network of institutional sites.[636]

In a multicenter trial, PCRC researchers examined the safety of discontinuing statin therapy in patients with advanced, life-limiting illness. The study showed no significant differences in mortality between patients who had discontinued statin therapy and those who had not. The patients who discontinued statins also reported improved quality of life and had lower health care costs.[637]

NINR designed an evidence-based campaign, *Palliative Care: Conversations Matter®*, 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.[638] The first phase of the campaign focused on health care providers and offered evidence-based materials to help providers discuss palliative care with pediatric patients and their families. The campaign's second phase focused on providing resources, such as brochures, for patients and families to increase awareness and empower them to begin a dialogue with health care providers. The Institute hopes that the campaign will increase the use of palliative care for children and teens living with serious illnesses.

In addition to the CFS workshop mentioned previously, in FY 2014, ODP coordinated a P2P workshop, "The Role of Opioids in the Treatment of Chronic Pain."[639] Results of this workshop have been used to inform other federal efforts to address the opioid epidemic.

In October 2014, NIAMS hosted "The Role of Disc Degeneration in Low Back Pain," a scientific roundtable to discuss the opportunities and challenges involved in understanding the mechanisms

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[634] https://painconsortium.nih.gov/nih_pain_programs/coepes.html.
[635] Law AS, et al. *J Dent Res* 2015;94(3 Suppl):37S-43S. PMID: 25355775.
[636] http://palliativecareresearch.org/.
[637] Kutner JS, et al. *JAMA Intern Med* 2015;175(5):691-700. PMID: 25798575.
[638] http://www.ninr.nih.gov/newsandinformation/conversationsmatter/conversations-matter-newportal#.Vz9WRvkrJD8.
[639] https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/opioids-chronic-pain.

underlying chronic back pain; identifying predictive markers of chronic back pain so that appropriate preventive strategies can be undertaken; and developing methodologies and model systems for identifying and studying disease subtypes and for testing potential treatments. The roundtable led to the release of two program announcements, using the R01 and R21 funding mechanisms, called Accelerating Research on Intervertebral Disc (ARID).[640,641]

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 becomes thick and sticky, so that the mucus builds up in the lungs and blocks the airways. This buildup of mucus makes it easy for bacteria to grow, leading 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.[642]

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, though many of them not know it.

NIH research on CF is varied, ranging from basic to clinical research. In 2014, NHLBI launched a new program to develop cell-based systems, grown from individual patients' cells, to mimic a patient's biology and reveal which drugs would work best for that patient. Such cell-based systems are needed because genetic testing alone cannot guide treatment; even inpatients with the same mutation sequence, disease severity can vary significantly. Thus, for clinicians choosing among the many emerging drugs, a cell-based model would more accurately capture how an individual patient's body would react. In addition, clinicians treating young children with CF could potentially use a cell model to predict treatment outcomes or delay or prevent the onset of disease.[643]

Another NHLBI initiative, launched in 2015, will fund collaborations among researchers studying aberrant fibrosis in different organ systems. Aberrant, or pathological, fibrosis is the development of excessive, damaging fibrous connective tissue in organs and can lead to organ failure. It is hoped that collaborations between researchers focused on fibrosis in different organ systems will enable development and sharing of common tools, accelerate scientific discovery, and reduce research costs.[644]

In studies in human cells and mice, NHLBI-funded investigators recently used nanoparticles linked to synthetic nucleic acids—the building blocks for DNA—to repair the most common mutation associated

[640] https://grants.nih.gov/grants/guide/pa-files/PA-16-096.html.
[641] https://grants.nih.gov/grants/guide/pa-files/PA-16-097.html.
[642] https://www.nhlbi.nih.gov/health/health-topics/topics/cf.
[643] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-027.html.
[644] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-003.html.

with CF. Further refinement of this approach to gene editing could result in a method for treating the disease.[645] Other NHLBI-funded researchers used genome-wide association analysis to identify five genetic modifiers of lung disease severity in CF, a finding that may lead to new therapeutic targets and allow for more individualized treatment.[646]

Dental 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 and older have some form of periodontal disease[647] and that tooth decay is the most common chronic disease among children ages 6 to 19—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.

The amount of dental caries (cavities) an individual experiences is related to the interplay of oral health behaviors, environmental factors, and genetic factors. In a study of the association of caries with genetic variations in four tooth enamel genes, daily tooth brushing, and home water fluoride concentration, dental caries were associated with variants in two of the genes. Moreover, there was evidence of an interaction between home fluoride exposure and enamel genes; for certain genetic variants, experiencing dental caries was associated with a genetic variant only in the absence of home fluoride exposure.[648]

A type of oral bacteria, *Streptococcus mutans*, that is the main cause of dental caries is also implicated in infective endocarditis (inflammation of the heart) and may contribute to other conditions, such as hemorrhagic stroke and atherosclerosis. NIDCR researchers demonstrated that *S. mutans* invades oral epithelial cells using a protein called Cnm, which also facilitates the invasion of human coronary artery endothelial cells. These results confirm Cnm's importance as a colonization factor for the oral cavity as well as a primary virulence factor in systemic disease.[649]

Chronic periodontal disease is a common multifactorial disease, involving behavioral, lifestyle, systemic, and genetic risk factors. However, the genetic basis for this disease is not well understood. Researchers re-analyzed genome-wide association data from a large dataset and identified six genes in four genomic regions, including two novel findings, for chronic periodontitis. The study demonstrates that comprehensive analytic approaches may extract additional information from such data, providing important leads for follow-up studies to understand the role of genetic factors in chronic periodontitis.[650]

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[645] McNeer N, et al. *Nat Commun* 2015; 6:6952. PMID: 4480796
[646] Corvol H, et al. *Nat Commun* 2015;6:8382. PMID: 26417704.
[647] https://www.cdc.gov/OralHealth/periodontal_disease/.
[648] Shaffer JR, et al. *Hum Genet* 2015;134(2):159-67. PMID: 25373699.
[649] Miller JH, et al. *Infect Immun* 2015;83(5):2001-10. PMID: 25733523.
[650] Rhodin K, et al. *J Dent Res* 2014;93(9):882-90. PMID: 25056994.

NIDCR co-funds the oral health component of NHANES, which CDC administers. NHANES findings are typically released by CDC as written data briefs. In addition to co-authoring data briefs on the latest NHANES oral health statistics, NIDCR and CDC dental epidemiologists presented live webinars in March and May of 2015. The first webinar was on the oral health of children and adolescents; the second presented data on adults and seniors. Hundreds of public health professionals, policymakers, and members of the news media viewed the webinars and participated in Q&A sessions with the presenters. These webinars gave NIDCR and CDC stakeholders better access to and understanding of the latest data on the oral health status of Americans and resulted in news articles in the dental trade press and *The New York Times*.[651,652,653]

NIDCR-supported investigators have shown that a molecule called DEL-1 (developmental endothelial locus 1) that is found in the mouth regulates immune cell activity in periodontal disease. In a mouse model, removing this protein causes periodontal disease and restoring it cures the disease, suggesting that DEL-1 could be valuable as a treatment for periodontal disease in humans. Local administration of human DEL-1 to the gums of monkeys with periodontitis significantly reduced periodontal inflammation, tissue destruction, and bone loss, compared with control animals. The ability of DEL-1 to prevent inflammatory cell recruitment to the teeth and gums and to inhibit bone loss paves the way for the development of a new class of therapeutics for treating periodontitis and perhaps other inflammatory disorders.[654]

Lipoxins are a unique class of naturally occurring lipid mediators that can control the resolution of inflammation. NIDCR is supporting the development of an oral rinse that includes a lipoxin analog for the topical treatment of gingivitis. After four years of preclinical work, a clinical trial for the treatment of gingivitis began enrolling patients in 2015. If successful, this drug may become a useful treatment for gingivitis and other oral inflammatory conditions, such as periodontitis.

Children with a rare inherited immune disorder called leukocyte adhesion deficiency type I (LAD-I) have frequent microbial infections, including severe, early-onset periodontal disease. NIDCR scientists completed the first comprehensive characterization of the subgingival bacterial communities in LAD-I patients and demonstrated that the bacteria can serve as triggers for periodontal inflammation by transferring bacterial products into tissues.[655]

Temporomandibular disorders are conditions that cause pain and dysfunction in the jaw joint and the muscles that control jaw movement. Another NIDCR-supported effort, the International Research Diagnostic Criteria for Temporomandibular Disorders (RDC-TMD) Consortium, provided the investigative framework for researchers from North America, Europe, and Australia to develop the first evidence-based diagnostic criteria to help health professionals better diagnose TMDs. These NIDCR-supported

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[651] http://well.blogs.nytimes.com/2015/03/05/untreated-dental-decay-is-falling-among-children/?_r=0.
[652] https://www.cdc.gov/nchs/data/databriefs/db191.pdf.
[653] https://www.cdc.gov/nchs/data/databriefs/db197.pdf.
[654] Shin J, et al. *Sci Transl Med* 2015;7(307):307ra155. PMID: 26424570.
[655] Moutsopoulos NM, et al. *Sci Transl Med* 2014;6(229) 229ra40. PMID:24670684.

investigators developed examination specifications in support of the diagnostic criteria, formed the validation project research group, and conducted reliability assessments.[656,657]

Diabetes

Diabetes, a disease that occurs when a person's blood glucose (blood sugar) is too high, is the seventh leading cause of death in the U.S. [658] Blood glucose 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.[659] Around 29 million Americans suffer from diabetes[660] and are at risk for the serious health complications it causes, including heart disease, blindness, kidney failure, and lower-extremity amputations.

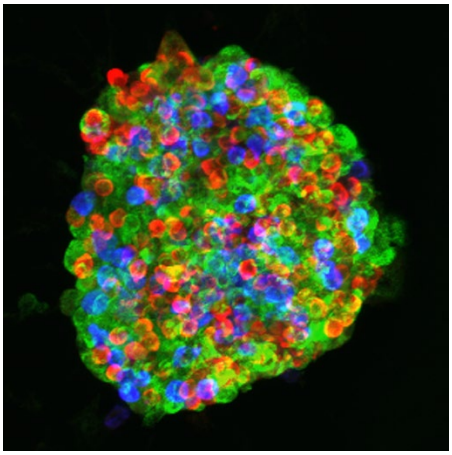

Figure 31. A human pancreatic islet, which contains many different cell types, including insulin-producing beta cells (green) and glucagon-producing alpha cells (red). Credit: Alvin Powers, M.D., and Marcela Brissova, Ph.D., Vanderbilt University.

The most common types of diabetes are type 1, type 2, and gestational diabetes. 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. Gestational diabetes develops in some women when they are pregnant and needs to be managed to help prevent complications for the mother

[656] https://ubwp.buffalo.edu/rdc-tmdinternational/tmd-assessmentdiagnosis/dc-tmd/
[657] Schiffman E, et al. *J Oral Facial Pain Headache* 2014;28(1):6-27. PMID: 24482784.
[658] https://www.cdc.gov/diabetes/basics/index.html.
[659] https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes.
[660] https://www.cdc.gov/diabetes/basics/index.html.

and offspring during delivery. Gestational diabetes usually resolves with delivery, but women who have had gestational diabetes have a greater chance of developing type 2 diabetes later in life.[661]

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.

Understanding Prevalence, Risk Factors, and Underlying Biology

In the Search for Diabetes in Youth (SEARCH) study led by CDC and NIDDK, researchers revealed that an estimated 167,000 young people (under age 20) in the U.S. had type 1 diabetes in 2009, an increase of more than 21 percent in eight years. SEARCH also found that some of this increase in prevalence is explained by a 2.72 percent annual increase in the number of non-Hispanic White youth (the racial and ethnic group with the highest prevalence of type 1 diabetes) who were diagnosed with type 1 diabetes from 2002 through 2009. SEARCH data also demonstrated that type 1 diabetes is becoming more common in Hispanic, Black, and Asian/Pacific Islander youth.[662,663,664] More updates on NIH diabetes research relating to health disparities are available in the minority health and health disparities section of this chapter.

Figure 32. An estimated 167,000 youth in the U.S. had type 1 diabetes in 2009, an increase of more than 21 percent in 8 years. Credit: istockphoto.com.

The Environmental Determinants of Diabetes in the Young (TEDDY) study is an NIDDK-led study to identify environmental factors that trigger or protect against type 1 diabetes in genetically susceptible individuals. The TEDDY study, in collaboration with NIAID, NIEHS, and NICHD, is currently following more than 6,000 high-risk newborns until they are 15 years old, collecting dietary and health data and stool, blood, and other samples. A significant -omics effort is underway to address questions related to the

[661] https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes.
[662] Pettitt DJ, et al. *Diabetes Care* 2014;37(2):402-8. PMID: 24041677.
[663] Dabelea D, et al. *JAMA* 2014;311(17):1778-86. PMID: 24794371.
[664] Lawrence JM, et al. *Diabetes* 2014;63(11):3938-45. PMID: 24898146.

cause and course of autoimmunity and type 1 diabetes, including metabolomics, proteomics, and studies of the microbiome and virome.[665]

NIEHS-supported research is investigating the role of environmental chemicals that disrupt the circadian hormone melatonin, potentially altering the homeostatic balance of glucose metabolism and insulin release and leading to type 2 diabetes and metabolic disorders.

The interplay of environmental and genetic factors is also important in the development of type 2 diabetes. In an NIEHS-funded study, researchers combined three lines of evidence—diet-induced epigenetic dysregulation in mice, replication of this dysregulation in adipose samples to identify regions where these epigenetic changes are conserved in humans, and human clinical risk evidence—to identify genes implicated in development of type 2 diabetes through epigenetic mechanisms related to insulin resistance and obesity. [666]

NIDDK-funded research found that subtle genetic differences at thousands of peroxisome proliferator-activated receptor gamma (PPARγ) DNA binding sites (in both mice and humans) that affect metabolism may account for variations in the effects of anti-diabetes drugs that act on PPARγ receptors.[667] In mice, ERK/MAP kinases phosphorylate adipose PPARγ, triggering insulin resistance, and MAPKK inhibitors restore insulin sensitivity, suggesting a possible new approach to treating type 2 diabetes.[668] In a 2015 NIDDK-funded study, researchers identified a protein, neuromedin U, that may restrain insulin production, particularly during fasting.[669]

NIDDK-funded researchers have also found that a gene linked to risk for type 1 diabetes in human studies plays a role in mitochondrial recycling in mice. Mouse beta cells that lack *Clec16a* have more mitochondria, but less mitochondrial activity, and produce less insulin in response to rising blood glucose levels than do normal beta cells. This could explain why people with a common mutation in *CLEC16A* have poorer insulin response than people with other variants of the gene. Researchers found that mouse beta cells lacking *Clec16a* showed signs of cellular stress that might make them more susceptible to a disease-initiating autoimmune attack, suggesting a possible way that this defect might lead to type 1 diabetes.[670]

Other mutations might offer some protection against the development of diabetes. NIH-funded researchers examining multiple different ethnic populations have identified rare mutations in the gene *SLC30A8* that appear to significantly reduce risk for type 2 diabetes. This suggests that medically inactivating *SLC30A8* or the protein it encodes could provide an effective way to treat or prevent the disease.

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[665] www.teddystudy.org.
[666] Multhaup ML, et al. *Cell Metab* 2015;21(1):138-49. PMID: 25565211.
[667] Soccio RE, et al. *Cell* 2015;162(1):33-44. PMID: 26140591.
[668] Banks AS, et al. *Nature* 2015;517(7534):391-5. PMID: 25409143.
[669] Alfa RW, et al. *Cell Metab* 2015;21(2):323-33. PMID: 25651184.
[670] Soleimanpour SA, et al. *Cell* 2014;157(7):1577-90. PMID: 24949970.

The diabetes field has benefitted from several emerging methods. NIBIB researchers recently applied a new nanoscale imaging technology called serial block-face scanning electron microscopy (SBF-SEM) to observe the structure of pancreatic islet cells. SBF-SEM can generate high-resolution images of large tissue samples at great detail at several levels, from an entire islet down to subcellular hormone-secreting vesicles within cells. The imaging technology offers the ability to quantify the structure of islets for study at different stages of development quickly and accurately and to compare normal and diseased islet models.[671,672]

One of the complications associated with diabetes is diabetic retinopathy. Researchers funded through NEI have discovered a role for dopamine (DA), a chemical synthesized in neurons and used as a messenger to communicate between cells, in early diabetic retinopathy and have identified potential therapies to prevent vision loss. Investigators previously found that diabetes leads to loss of DA in the retina, but this finding's significance for diabetic retinopathy was not well understood. Using rodent models of diabetes, NEI investigators found the drop in DA levels correlated with the onset of damage to the retina. Furthermore, the researchers were able to reverse visual deficits by treating the animals with drugs that supplemented low DA in rodent models.[673]

The Accelerating Medicines Partnership Type 2 Diabetes (AMP-T2D) Program, spearheaded by NIDDK, 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 100 genes that are known to affect type 2 diabetes risk and on how those genes 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. 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 Foundation for the NIH.[674,675,676]

Improving Treatment and Prevention

NIH is funding several avenues of cutting-edge research into diabetes treatment. The Clinical Islet Transplantation Consortium, which is co-led by NIDDK and NIAID, is conducting clinical and mechanistic studies in islet transplantation, with or without accompanying kidney transplantation, for the treatment of difficult-to-control type 1 diabetes. The consortium has completed a pivotal (Phase III) islet transplantation trial (without kidney transplantation); the results are under review by FDA and are expected to support biologic license applications for purified human pancreatic islets.[677]

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[671] Pfeifer CR, et al. *J Struct Biol* 2015;189(1):44-52. PMID: 25448885.
[672] Shomorony A, et al. J Microsc 2015;259(2):155-64. PMID: 26139222.
[673] Aung MH, et al. *J Neurosci* 2014;34(3):726-36. PMID: 24431431.
[674] http://www.type2diabetesgenetics.org/.
[675] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-003.html.
[676] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-503.html.
[677] http://www.citisletstudy.org/.

Researchers supported by NIDDK's Beta Cell Biology Consortium (BCBC) made a breakthrough discovery, listed as one of *Science's* Top 10 Breakthroughs of 2014, of a large-scale method to produce beta cells from human iPSCs; when transplanted into a mouse model of type 1 diabetes, these stem cell–derived beta cells produced significant amounts of insulin in response to glucose and protected the animals against hyperglycemia. This advance provides a possible source for large quantities of beta cells for therapeutic use; however, additional research will be required to identify ways to protect these cells from autoimmune attacks in people with type 1 diabetes. To capitalize on the BCBC's success, in 2014, NIDDK launched a new team science program, the Human Islet Research Network (HIRN), to pursue innovative strategies to protect and replace beta cells in people with diabetes.[678, 679]

NIDDK-funded researchers have found that harmine, an alkaloid, promotes beta cell replication in mice and in human tissue culture experiments. This observation offers a potential new therapeutic avenue for expanding beta cell mass and restoring the ability of people with diabetes to produce their own insulin, although safety and efficacy in humans remain uncertain.[680]

There has also been tremendous progress toward the development of artificial pancreas technology that automatically links glucose monitoring and insulin delivery. Such technology could help people with type 1 diabetes achieve recommended levels of blood glucose control and alleviate a tremendous amount of the burden associated with current management strategies. In one NIDDK study, scientists showed that adolescents with type 1 diabetes who used an artificial pancreas system at home, unsupervised and overnight, for 21 nights had fewer episodes of nighttime hypoglycemia (dangerously low blood glucose levels) and better glucose control during the day and night. [681] In another real-world study, researchers tested a bihormonal (insulin and glucagon) "bionic pancreas" in both adults and adolescents and found that participants using this smartphone-controlled device nearly all stayed within recommended glucose control targets and had fewer episodes of hypoglycemia than a control group using insulin pump–based treatment.[682] NIDDK is now building on these and other successes and supporting advanced clinical trials that could pave the way toward FDA approval of artificial pancreas devices.

New findings from NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its followup, the Epidemiology of Diabetes Interventions and Complications Study (EDIC), demonstrated that a short period of intensive glucose control early in life prevents or delays heart, kidney, and eye complications for decades in people with type 1 diabetes. Intensive glucose control during the initial DCCT study also resulted in a 33 percent reduction in deaths 20 years after the trial ended. These results further

[678] https://hirnetwork.org.
[679] Pagliuca FW, et al. *Cell* 2014;159(2):428-39. PMID: 25303535.
[680] Wang P, et al. *Nat Med* 2015;21(4):383-8. PMID: 25751815.
[681] Hovorka R, et al. *Diabetes Care* 2014;37(5):1204-11. PMID: 24757227.
[682] Russell SJ, et al. *N Engl J Med* 2014;371(4):313-25.PMID: 24931572.

emphasize the importance of good early glucose control, which has a prolonged benefit in reducing mortality.[683,684,685,686,687]

Type 1 Diabetes TrialNet is an NIDDK-led international clinical trials network that screens large numbers of individuals and conducts trials of agents to prevent type 1 diabetes in at-risk people and to slow progression of the disease in people who are newly diagnosed. Blood tests can accurately identify relatives of people with type 1 diabetes who are at high or moderate risk of developing the disease within five years. This has enabled TrialNet to launch clinical trials of promising prevention strategies, three of which (oral insulin, abatacept, and teplizumab) are currently ongoing; the oral insulin trial has completed recruitment. The network also recently launched two new trials in newly diagnosed people, one testing antithymocyte globulin/granulocyte-colony stimulating factor and another testing tocilizumab.[688]

The Restore Insulin Secretion (RISE) consortium includes studies assessing the hypothesis that aggressive glucose lowering in people with prediabetes and early type 2 diabetes will lead to recovery of beta-cell function that will be sustained after treatment. Another effort will compare bariatric surgery to treatment with metformin, the most common first-line medication for treating type 2 diabetes.[689]

The D2d (Vitamin D and type 2 Diabetes) study, led by NIDDK with additional support from ODS, will determine whether vitamin D is safe and effective in delaying onset of type 2 diabetes in people at risk and will improve understanding of how vitamin D affects glucose metabolism.[690] Another NIDDK-led study (with additional support from CDC, NHLBI, NCI, ORWH, NIA, and NEI), the Diabetes Prevention Program Outcomes Study (DPPOS), is following participants in the landmark Diabetes Prevention Program (DPP) to determine the long-term outcomes and efficacy of the DPP interventions (lifestyle changes or metformin). The DPPOS has found that not only does the lifestyle intervention continue to be effective for at least 14 years, its health benefits are so significant that despite its cost (as originally designed), it reduces the need for other health care to the point that its 10-year net cost is very low. Although metformin confers less benefit than lifestyle changes, it is so inexpensive that it actually saves a modest amount of money. The study has also made other important findings, including the pharmacogenomic characterization of a gene that influences the transport and effectiveness of metformin, currently the most important medication in the treatment of type 2 diabetes. The next phase of DPPOS, starting in 2016, will examine the potential efficacy of metformin in preventing cancer and cardiovascular disease.[691]

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[683] https://portal.bsc.gwu.edu/web/edic/home.
[684] DCCT/EDIC Research Group, et al. *N Engl J Med* 2015;372(18):1722-33. PMID: 25923552.
[685] Lachin JM, et al. *Diabetes Care* 2014;37(1):39-43. PMID: 24356596.
[686] de Boer IH, et al. *Diabetes Care* 2014;37(1):24-30. PMID: 24356594.
[687] Writing Group for the DCCT/EDIC Research Group, et al. *JAMA* 2015;313(1):45-53. PMID: 25562265.
[688] http://www.diabetestrialnet.org/.
[689] https://rise.bsc.gwu.edu/web/rise/home.
[690] http://www.d2dstudy.org/.
[691] https://dppos.bsc.gwu.edu/web/dppos/dppos.

The Glycemia Reduction Approaches in Diabetes: An Effectiveness Study (GRADE), led by NIDDK with additional support from NHLBI, is comparing the long-term benefits and risks of four widely used diabetes drugs in combination with metformin. The study will compare drug effects on glucose levels, adverse effects, diabetes complications, and quality of life over an average of nearly 5 years.[692]

Research has shown that good control of blood glucose levels is critically important to preventing long-term complications of type 1 diabetes. However, achieving good blood glucose control is challenging, so NIDDK supports behavioral research to help people with type 1 diabetes and their families better manage the disease and maintain good quality of life. In 2014, new research was funded in response to two FOAs toward improving disease management: Understanding Barriers and Facilitators to Type 1 Diabetes Management in Adults;[693] and Improving Diabetes Management in Young Children with Type 1 Diabetes,[694] which was also reissued for FY 2015 funding.[695]

Exercise is generally recommended for patients with diabetes, but people with diabetes-related nerve damage (peripheral neuropathy) have historically been told to avoid weight-bearing exercise out of concern for possible injury of parts of the body weakened or numbed by the nerve damage. However, an NICHD-supported clinical trial has shown that patients who increased the number of steps they took by a relatively modest amount, for several walks, showed improvement in the distance they could walk in six minutes and their daily average step totals, while people in the control group, doing non–weight-bearing exercise, showed improvement in hemoglobin A1c, an indicator of blood sugar control. The results suggest that both types of exercise could be recommended in individualized combinations for diabetes patients with peripheral neuropathy.[696]

An NIH-supported clinical trial compared three drugs for diabetic macular edema, a complication of diabetes that causes abnormal blood vessels to grow into the retina. All three drugs reversed vision loss in diabetic patients. While all three drugs resulted in similar visual improvements in patients with mild vision loss at the start of the trial, one drug, aflibercept (Eylea), outperformed the other two, bevacizumab (Avastin) and ranibizumab (Lucentis), when baseline vision loss was moderate or severe (20/50 or worse on an eye chart). Investigators found no major differences in the safety of the three drugs. This comparative effectiveness study empowers doctors and patients to make personalized decisions about treatment.[697]

The NIDDK-led Preventing Early Renal Function Loss in Diabetes clinical trial completed recruitment and is examining whether the drug allopurinol—currently used for the treatment of gout—could preserve kidney function in people with type 1 diabetes who are at high risk of kidney disease. The trial has the potential to identify an inexpensive approach to preserving kidney function in people with type 1 diabetes. If effective, allopurinol may also be relevant to preserving kidney function in the larger

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[692] https://grade.bsc.gwu.edu/web/grade/home.
[693] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-023.html.
[694] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-022.html.
[695] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-022.html.
[696] Mueller MJ, et al. *Arch Phys Med Rehabil* 2013;94(5):829-38. PMID 23276801.
[697] Jampol LM, et al. *JAMA Ophthalmol* 2015;133(9):983-4. PMID: 26087135.

population of people with type 2 diabetes. This study was unlikely to be supported by the private sector because it is testing a generic drug.[698]

NIDDK funds translational research for the prevention and control of diabetes, as well as several Centers for Diabetes Translation Research. These centers fund postclinical translational research based on past successful diabetes clinical trials, including projects to lower the cost and increase the availability of lifestyle interventions to prevent diabetes based on the landmark DPP clinical trial.[699,700,701]

Nearly half of all cases of gestational diabetes may be preventable, according to an NICHD analysis. A low-risk lifestyle during pregnancy—that is, maintaining a healthy body weight, consuming a healthy diet, not smoking, and exercising at least 150 minutes a week—is related to a substantially lower risk of developing gestational diabetes, according to an NICHD analysis of data from a long-term study that included more than 10,000 women. Women at low risk for all four factors had more than 80 percent less risk of gestational diabetes, which can have long-term health effects for both mothers and children. A combination of the four risk factors may account for nearly half of all cases of gestational diabetes.[702]

Governments, schools, insurers, and communities are making policy changes in hopes of reversing trends toward obesity and diabetes, but there is limited evidence about how well these large-scale changes in healthcare work to improve diabetes prevention or treatment. To answer these questions, NIDDK is funding the research initiative Evaluating Natural Experiments in Healthcare to Improve Diabetes Prevention and Treatment.[703]

Another NIDDK program, Pragmatic Research in Healthcare Settings to Improve Diabetes and Obesity Outcomes, supports research testing practical, sustainable approaches to improve diabetes and obesity prevention and treatment in routine healthcare settings. The program's goal is to obtain results that will improve routine healthcare practice and inform healthcare policy for the prevention or management of these conditions.[704]

The National Diabetes Education Program (NDEP), co-led by CDC and NIDDK and involving more than 200 public and private partners, disseminates evidence-based educational materials on diabetes. For example, the program encourages people to take "small steps" to prevent type 2 diabetes; it also promotes the importance of comprehensive diabetes control in its *Control Your Diabetes. For Life*. educational campaign.[705] Materials are tailored for minority groups at high risk of developing type 2 diabetes. NDEP released *Guiding Principles for the Care of People with and at Risk for Diabetes*, a

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[698] http://www.perl-study.org/.
[699] https://grants.nih.gov/grants/guide/pa-files/PAR-13-366.html.
[700] https://grants.nih.gov/grants/guide/pa-files/PA-13-352.html.
[701] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-10-009.html.
[702] Zhang C, et al. *BMJ* 2014;349:g5450. PMID: 25259649.
[703] https://grants.nih.gov/grants/guide/pa-files/PAR-13-365.html.
[704] https://grants.nih.gov/grants/guide/pa-files/PAR-13-366.html.
[705] https://www.niddk.nih.gov/health-information/health-communication-programs/ndep/partnership-community-outreach/campaigns/control-diabetes-life/Pages/controlyourdiabetesforlife.aspx.

document that focuses on areas of general agreement and consensus on proven therapies to help clinicians help their patients with and at risk for diabetes achieve better outcomes.[706]

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 (GERD), are common; others, such as genetic forms of liver disease, are quite rare. Collectively, digestive disease 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 32 million visits to a doctor or emergency room in 2013 in the U.S. were due to diseases within the digestive system.[707] NIH's research spans the breadth of the many different digestive diseases affecting Americans, from investigating the diseases' biological and basic underpinnings to improving they are treated and prevented.

Understanding Prevalence, Risk Factors, and Underlying Biology

Most cases of celiac disease in the U.S. go undiagnosed, although early detection and intervention are likely to benefit patients. In an effort to address these realities, a study released in 2015 evaluated the effectiveness of testing patients who have symptoms of irritable bowel syndrome for celiac disease. The study showed that symptoms of celiac disease and IBS are common in U.S. white populations and that, contrary to current recommendations in other countries, testing for celiac disease in patients with IBS may not be more effective than a general population-based screening.[708]

A study released in 2014 analyzed data from the TEDDY consortium and found that more than one quarter of children with two copies of a specific genetic variant develop an early sign of celiac disease by age 5. This finding could help inform future recommendations for celiac disease screening in young children and could pave the way to early personalized prevention and treatment approaches based on genetic risk. The study also suggests the need for further research to understand the environmental factors that influence the development of celiac disease in people who are genetically susceptible, another area the TEDDY study is addressing.[709,710]

The Inflammatory Bowel Disease (IBD) Genetics Consortium is a major driver of NIDDK's research program on the role of genetic factors in the development of Crohn's disease and ulcerative colitis. The Consortium is part of a 15-member international consortium that has helped increase the power of analyses to enable discovery of additional risk variants for IBD. In a study released in 2015, researchers in the IBD Genetics Consortium examined human leukocyte antigen (HLA) genes in more than 32,000 adults with Crohn's disease or ulcerative colitis and identified genetic variants that are highly associated

[706] www.ndep.nih.gov.
[707] https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2013_namcs_web_tables.pdf.
[708] Choung RS, et al. *Clin Gastroenterol Hepatol* 2015;13(11):1937-43. PMID: 25987301.
[709] Liu E, et al. *N Engl J Med* 2014;371(1):42-9. PMID: 24988556.
[710] https://www.nih.gov/news-events/news-releases/gene-type-confers-26-percent-chance-early-celiac-sign-age-5.

with both diseases. The findings point to specific genetic traits that could be important in the development of IBD.[711]

In an NIDDK-funded study released in 2015, scientists found that patients with IBD had a greater variety of viruses in their digestive systems than healthy volunteers did, suggesting that viruses likely play a role in Crohn's disease and ulcerative colitis and supporting further investigation of these viruses as a potential diagnostic tool for IBD.[712] Other research with gut viruses in mice suggests that a particular type of virus can confer some of the same benefits to its host as gut bacteria do. This virus was able to protect the guts of antibiotic-treated mice from further damage or death caused by a chemical agent used to mimic human IBD. The study demonstrated for the first time that a virus in the mouse intestinal tract could have beneficial effects on intestinal physiology, immune function, and disease protection similar to those granted by gut bacteria.[713]

In a mouse study released in FY 2014, scientists found that a well-known anti-cancer protein called retinoblastoma 1, or RB1, plays a surprising role in GI motility. When they deleted RB1 in certain cells of mice, the researchers unexpectedly found that the mice developed severe intestinal blockages that in some ways resembled the bowel obstructions experienced by humans with certain motility disorders. This study suggests that the RB1 protein is important for proper function of the enteric nervous system in mice, a finding that may help researchers understand the causes of GI motility disorders in humans.[714]

In FY 2015, NIDDK released a new initiative to support research on lymphatic vessel physiology, development, and pathophysiology related to health and diseases of the digestive system, kidney, and urinary tract organs.[715] In September 2015, NIDDK, NHLBI, NIAID, NEI, NCI, NICHD, and representatives of the Lymphatic Education & Research Network cosponsored a symposium for lymphatic system researchers and organ experts to explore the function of the lymphatic system in organ physiology and pathology.

NIDDK-funded research from FY 2015 determined the mechanisms by which cells in the developing and renewing gut epithelium are programmed to establish and maintain the appropriate phenotypes, including support for progenitor cells and structures needed for nutrient absorption. Apparent differences in the factors involved in intestinal development compared with renewal of adult epithelium from stem cells could be exploited in the future to help direct repair of a damaged epithelium or construction of its replacement.[716,717]

In 2009, together with NIAID, NIDDK established the Intestinal Stem Cell Consortium (ISCC) to stimulate basic research through the development of new technologies to isolate, characterize, cultivate, and manipulate intestinal stem cells. In 2014, ISCC was recompeted and a new set of projects began,

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[711] Goyette P, et al. *Nat Genet* 2015;47(2):172-9. PMID: 25559196.
[712] Norman JM, et al. *Cell* 2015;160(3):447-60. PMID: 25619688.
[713] Kernbauer E, et al. *Nature* 2014;516(7529):94-8. PMID: 25409145.
[714] Fu M, et al. *J Clin Invest* 2013;123(12):5152-64. PMID: 24177421.
[715] https://grants.nih.gov/grants/guide/pa-files/PAR-15-306.html.
[716] Elliott EN, et al. *Development* 2015;142(12):2163-72. PMID: 26023099.
[717] San Roman AK, et al. *J Biol Chem* 2015;290(3):1850-60. PMID: 25488664.

including projects on pluripotent stem cells, the stem cell response to infection, regulation of the various stem cell populations that maintain the intestinal epithelium, and epigenetic control of stem cell activity.[718] Studies published by ISCC researchers in 2014 and 2015 shed light on using stem cells to grow functional intestinal tissue that was successfully transplanted into the mouse kidney capsule,[719] stem cells and cancer,[720] and genetic regulation of epithelial development and maturation from stem cells.[721]

An NIDDK-supported study published in 2015 and performed in cell and animal models highlighted the discovery of a plant toxin capable of causing changes resembling a rare pediatric liver disease called biliary atresia. Patients with biliary atresia have scarred and blocked bile ducts; left untreated, the disease can be fatal. Scientists analyzed samples from plants eaten by pregnant Australian sheep that had resulted in a disease similar to biliary atresia in newborn lambs. The researchers isolated a toxin, dubbed "biliatresone," that caused bile duct defects in zebrafish larvae and mouse cells. This discovery points to new directions for future research into means to prevent and treat this disease.[722]

In 2015, in partnership with NCI, NIDDK launched a new Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) to conduct studies of people with chronic pancreatitis, with the goal of improving understanding of disease processes and related outcomes, such as diabetes and pancreatic cancer.[723] NIDDK and NCI funded a grant in FY 2015 to support a pediatric pancreatitis consortium within the larger CPDPC. The work builds on a previous award that NIDDK supported in and before FY 2014 to form INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In search for a cure).[724]

Improving Treatment and Prevention

Two studies show how gut bacteria interact with diet and the host's immune and digestive systems to affect overall health. In a study published in 2014, scientists found that Bangladeshi children who are malnourished have gut bacterial communities that are "immature" or not typical for their ages, even several months after the children receive nutritional interventions.[725] In another study, researchers collected samples of fecal bacteria from severely undernourished infants and children living in Malawi and tested these bacteria in mice to identify a group of microorganisms that establish themselves in the gut during nutrient deficiency and damage the intestinal lining, limiting the body's ability to absorb nutrients and fend off disease.[726] These findings may help identify individuals at risk for persistent childhood undernutrition and design more effective therapeutic and preventive strategies for ameliorating this global problem.

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[718] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-012.html.
[719] Watson CL, et al. *Nat Med* 2014;20(11):1310-4. PMID: 25326803.
[720] Asfaha S, et al. *Cell Stem Cell* 2015;16(6):627-38. PMID: 26046762.
[721] Finkbeiner SR, et al. *Stem Cell Reports* 2015;pii-S2213-6711(15)00122-8. PMID: 26050928.
[722] Lorent K, et al. *Sci Transl Med* 2015;7(286):286ra67. PMID: 25947162.
[723] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-028.html.
[724] http://www.medicine.uiowa.edu/pediatrics/insppire/.
[725] Subramanian S, et al. *Nature* 2014;510(7505):417-21. PMID: 24896187.
[726] Kau AL, et al. *Sci Transl Med* 2015;7(276):276ra24. PMID: 25717097.

A team of NIH-funded scientists succeeded in reprogramming mature human skin cells into a type of liver cell that can repopulate the organ after liver failure in a mouse model. Although further experiments are needed before this cell technology can be applied to humans, it represents a major step toward being able to use cells from a patient's own body to heal their diseased liver. This technology could help to surmount current challenges, such as long wait times for donor organs and lifelong immunosuppressive therapy to prevent organ rejection.[727,728]

For a study released in 2014, scientists used a special type of mouse with human cells in its liver for a proof-of-concept study to predict which experimental drugs can cause liver failure and should not be tested in humans. Use of these preclinical animal models could reduce the chance that volunteers in clinical trials might be exposed to experimental drugs that could cause acute liver failure.[729]

A clinical trial testing a new drug specifically designed to treat a severe form of nonalcoholic fatty liver disease (NAFLD) that is on the rise in the U.S. and worldwide showed the drug's promise for reducing the disease, though some questions about its long-term safety remain. The Farnesoid X Receptor Ligand Obeticholic Acid in NASH [nonalcoholic steatohepatitis] Treatment (FLINT) trial was conducted as part of NIDDK's Nonalcoholic Steatohepatitis Clinical Research Network, with support from an industry partner, to test the synthetic bile acid obeticholic acid (OCA) as a potential treatment for severe NAFLD. Larger, longer-term studies are now underway to evaluate the drug's safety and effects on NAFLD.[730,731] In FY 2014, the NASH Clinical Research Network, which supports projects designed to longitudinally gather biospecimens and data of children and adults with NAFLD, was renewed.[732]

In a 2014 clinical trial to examine sphincterotomy, an endoscopic procedure used to relieve pain in cases of suspected sphincter of Oddi dysfunction (SOD) after gallbladder removal, researchers found that this risky procedure may not be effective. The procedure involves cutting the sphincter of Oddi, the small circular muscle that allows bile and pancreatic juice to flow into the intestine. The results of this trial suggest that sphincterotomy does not improve pain in cases of suspected SOD—a finding that could save patients from the burden of this procedure.[733]

In 2014, NIDDK continued to support the Childhood Liver Disease Research Network (ChiLDReN), which sponsors clinical and translational research to improve understanding of rare pediatric liver diseases.[734] A ChiLDReN study reported that infants with biliary atresia who received corticosteroid treatment after bile duct surgery did no better than those receiving surgery alone and in fact might be harmed due to an increased risk of complications.[735,736]

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[727] Zhu S, et al. *Nature* 2014;508(7494):93-7. PMID: 24572354.
[728] https://directorsblog.nih.gov/2014/03/04/impcs-cell-reprogrammers-take-aim-at-liver-disease/.
[729] Xu D, et al. *PLoS Med* 2014;11(4):e1001628. PMID: 24736310.
[730] https://www.nih.gov/news-events/news-releases/new-drug-common-liver-disease-improves-liver-health.
[731] Neuschwander-Tetri BA, et al. *Lancet* 2015;385(9972):956-65. PMID 25468160.
[732] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-503.html.
[733] Cotton PB, et al. *JAMA* 2014;311(20):2101-9. PMID: 24867013.
[734] https://childrennetwork.org/.
[735] Bezerra JA, et al. *JAMA* 2014;311(17):1750-9. PMID: 24794368.
[736] https://www.nih.gov/news-events/news-releases/steroids-after-surgery-do-not-help-infants-rare-liver-disease.

An initiative released in 2014 continued the work of the adult Acute Liver Failure Study Group (ALFSG), supporting projects for up to 5 years. The focus is on 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 of, treatment options for, and complications from ALF.[737]

Individuals who suffer from IBS experience a complex collection of symptoms, and there is no standard therapy to treat the full spectrum of symptoms associated with this disorder. A hormone called vasoactive intestinal peptide (VIP) has been identified as a potential drug target for several chronic inflammatory diseases, so researchers sought to explore the role VIP may play in IBS. By measuring VIP levels in both human participants and an animal model, researchers supported by the NINR IRP, NINDS, and NIDDK found that VIP expression was upregulated in IBS patients compared with healthy control participants, as were VIP protein levels in rats with induced colitis compared with control rats. These findings suggest that alterations in VIP expression may play a role in IBS, and future work could lead to new therapeutic options that target VIP for management of IBS symptoms.[738]

Eye Disease and Disorders of Vision

Diseases and disorders of the eye affect millions of Americans and create a significant burden both for those afflicted and for society at large. For example, more than 3.3 million Americans over age 40 are either legally blind or have low vision.[739] 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, and another 7.3 million are at risk for developing it.[740] 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 age 40 and above are estimated to have cataracts in one or both eyes. These and many other common ocular disease 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.

Understanding Prevalence, Risk Factors, and Underlying Biology

An international study of about 43,000 people has significantly expanded the number of genetic factors known to play a role in AMD. Researchers have now discovered 52 genetic variants associated with AMD. This NEI and NHGRI-funded study identified 16 new risk variants that had not previously been associated with AMD. The findings may help improve our understanding of the biological processes that lead to AMD and identify new therapeutic targets for potential drug development.[741]

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[737] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-504.html.

[738] Del Valle-Pinero AY, et al. *World J Gastroenterol* 2015;21(1):155-63. PMID: 25574088.
[739] https://www.cdc.gov/visionhealth/basics/ced/.
[740] https://www.cdc.gov/visionhealth/basics/ced/.
[741] Fritsche LG, et al. *Nat Genet* 2016;48(2):134-43. PMID: 26691988.

Leber hereditary optic neuropathy, one of the more common mitochondrial diseases, is caused by a mutation in a mitochondrial gene that interferes with energy transfer, leading to degeneration of retinal ganglion cells and deterioration of the optic nerve. NEI is conducting a gene therapy clinical trial for a mitochondrial eye disorders to better understand this condition.[742]

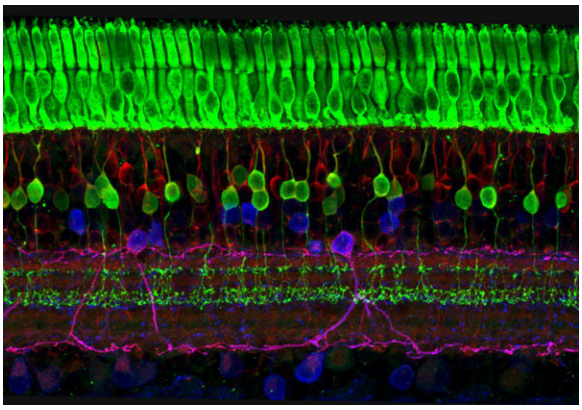

Figure 33. This image captures the many layers of nerve cells in the retina. The top layer (green) is made up of cells called photoreceptors that convert light into electrical signals to relay to the brain. Credit: Wei Li, NEI.

Geographic atrophy (GA), a late stage of AMD, is characterized by death of the retinal pigment epithelium (RPE) and eventual loss of photoreceptors in the retina, leading to blindness. Researchers trying to understand what leads a healthy cell into a death spiral are focusing on a complex of proteins called the inflammasome, which regulates the immune system's response to injury, toxins, or infection and, when activated, can lead to cell suicide. Patients with GA have reduced levels of an RNA processing enzyme called DICER1. Researchers demonstrated that in animal models, a DICER1 deficiency leads to toxic accumulation of RNA molecules called Alu elements, activating the enzyme caspase-8. Blocking caspase-8 prevented RPE cell death, suggesting a new potential therapeutic target for geographic atrophy.[743]

Improving Treatment and Prevention

Through the Regenerative Medicine Program, which leverages the NIH Common Fund and the NIH Eye Clinic, scientists are using iPSC technology to generate retinal tissue from patients with AMD.[744] This approach has resulted in patient-specific disease models in a dish, allowing researchers to understand causes of AMD, screen for drugs, and develop cell-based therapies. In FY 2014 and 2015, several papers were published and several patents obtained for methods to direct iPSCs to develop into RPE, the tissue that is destroyed in macular degeneration.[745,746] Preclinical studies are now underway, bringing this research one step closer to the clinic. Through this research, researchers are working to resolve scientific

[742] Lam BL, et al. *JAMA Ophthalmol* 2014;132(4):428-36. PMID: 24525545.
[743] Kim Y, et al. *Proc Natl Acad Sci* 2014;111(45):16082-7. PMID: 25349431.
[744] https://commonfund.nih.gov/stemcells/index.
[745] Blenkinsop TA, et al. Invest Ophthalmol Vis Sci. 2015 Nov;56(12):7085-99. PMID: 26540654.
[746] http://www.google.com/patents/WO2014121077A3?cl=en.

and regulatory hurdles so that other researchers can address conditions that may benefit from iPSC-based therapies.

Researchers are developing gene therapy to prevent a common form of AMD. About half of all cases of the disease result from an alteration in complement factor H (*CFH*), a gene that regulates immune responses, leading to a chronic state of inflammation in the eye. In the advanced stage of AMD, a process known as choroidal neovascularization (CNV) occurs: Abnormal blood vessels that leak blood and fluid develop, leading to severe central vision loss. In a mouse model of AMD, delivery of ***PRELP***, a gene known to inhibit CFH protein expression, greatly reduced CNV. Although preliminary, this approach could provide a treatment to prevent severe vision loss for many people with AMD.[747]

AMD causes significant impairment of central vision, making activities of daily living such as reading and driving difficult or impossible; it can also lead to severe depression. The Low Vision Depression Prevention Trial found that augmenting low vision rehabilitation with behavioral support from occupational therapists or mental health therapists reduced the incidence of depression by 50 percent compared with low vision rehabilitation alone. These results suggest that collaborative care between eye care professionals, therapists, and mental health practitioners can help reduce or prevent depression that accompanies AMD.[748]

Figure 34. A researcher examines eye tissue in a microscope. Credit: NEI.

In AMD and diabetic retinopathy, growth of abnormal blood vessels in the retina can cause blindness. New drugs have helped prevent and reverse some damage when injected into the eye every 4–8 weeks. But injections are uncomfortable and time-consuming, and they carry risks of infection and retinal damage. NEI investigators have developed a novel biocompatible nanoparticle drug delivery system based on a polymer that is broken down by ultraviolet (UV) light. Once injected into the eye, the delivery system can store a reservoir of drugs for months. Brief exposure to low-power light can noninvasively release drugs embedded in the polymer. Light-triggered release of the small molecule drug nintedanib suppressed blood vessel growth in rats for 10 weeks.[749]

[747] Birke MT, et al. *Gene Ther* 2014;21(5):507-13. PMID: 24670995.
[748] Rovner BW, et al. *Ophthalmology* 2014;121(11):2204-11. PMID: 25016366.
[749] Huu VA, et al. *J Control Release* 2015;200:71-7. PMID: 25571784.

Levodopa (L-dopa) is a well-known drug used to treat Parkinson's disease. In RPE, L-dopa down-regulates vascular endothelial growth factor, a protein that can abnormal blood vessel growth in AMD. By mining retrospective data, NEI investigators found that patients taking L-dopa, for Parkinson's or other diseases, had a lower incidence of AMD than did age-matched controls not taking the drug; patients taking L-dopa who did develop AMD had a later average age of onset. This suggests that L-dopa may prevent or delay AMD and could be repurposed for people at risk for AMD.[750]

Researchers showed nucleoside reverse transcriptase inhibitors (NRTIs), commonly used to treat HIV, block cellular components of the inflammation pathway in rodents' eyes, reducing cell death and damage in models of dry and wet macular degeneration. These FDA-approved drugs could be repurposed to treat AMD and a host of other inflammatory diseases.[751]

The cornea, the eye's transparent, self-renewing outer surface, protects the eye from the environment. Limbal stem cells (also called corneal epithelial stem cells) resident in the cornea are key to wound healing and repair. Corneal transplants and grafts are standard therapies, but it is difficult to determine whether a potential graft contains an adequate supply of limbal stem cells. NEI investigators identified the *ABCB5* gene as a central biomarker for renewal of corneal stem cells, allowing clinicians to improve corneal transplant surgeries by gauging the regenerative potential of donor tissue.[752]

The lens is a transparent structure that focuses light in the eye. Its clarity is due to a crystal-like arrangement of proteins in lens cells, but over time these proteins can break down and form clumps, leading to a cloudiness known as a cataract. Cataracts are the leading cause of vision loss, reducing vision in 50 percent of people over age 70, but the condition can be treated with surgery to replace the lens. Recent studies into alternatives to surgery have identified small molecules that can bind and stabilize lens proteins, restoring transparency to the lens in animal models. These agents could be delivered via eye drops, potentially eliminating the need for costly surgery.[753]

Myopia, also known as near-sightedness, is a common type of refractive error that makes close objects appear clearly but distant objects appear blurry. Myopia occurs in nearly one third of the population, with most cases developing in childhood; it can be corrected with contact lenses and eyeglasses. Previous studies suggest that myopia progression is caused by poorly focused images on the back of the retina, causing the eye to lengthen in an effort to focus and resulting in myopia. Bifocal contact lenses may reduce retinal defocus by offering greater clarity in near- and far-sightedness, thus reducing the stimulus to eye elongation and myopia progression. NEI recently launched the Soft Bifocal Contact Lens Myopia Control Study, a randomized clinical trial designed to evaluate whether such lenses can slow the progression of myopia in children.[754]

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[750] Brilliant MH, et al. *Am J Med* 2016;129(3):292-8. PMID: 26524704.
[751] Fowler BJ, et al. *Science* 2014;346(6212):1000-3. PMID: 25414314.
[752] Ksander BR, et al. *Nature* 2014;511(7509):353-7. PMID: 25030174.
[753] Makley LN, et al. *Science* 2015;350(6261):674-7. PMID: 26542570.
[754] https://clinicaltrials.gov/ct2/show/NCT02255474.

Another team of NEI scientists developed a contact lens that offers long-term, chronic administration of pressure-reducing drugs to control glaucoma. This approach resolves the challenge of treatment compliance in glaucoma patients who forget or otherwise fail to use their daily medications.[755]

In 2015, NEI investigators launched the first-ever human gene therapy trial for the vision disorder X-linked retinoschisis (XLRS). This genetic eye disease causes the layers of the retina, the light-sensitive neural tissue in the back of the eye, to split. XLRS is diagnosed in early childhood and is currently untreatable. The gene implicated in this disease, Retinoschisin 1, encodes a protein that acts like double-sided adhesive to keep retinal layers intact.[756]

Kidney Diseases

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.[757] Millions of Americans suffer from kidney diseases, including chronic kidney disease, which affects an estimated 30 million adults.[758] 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.

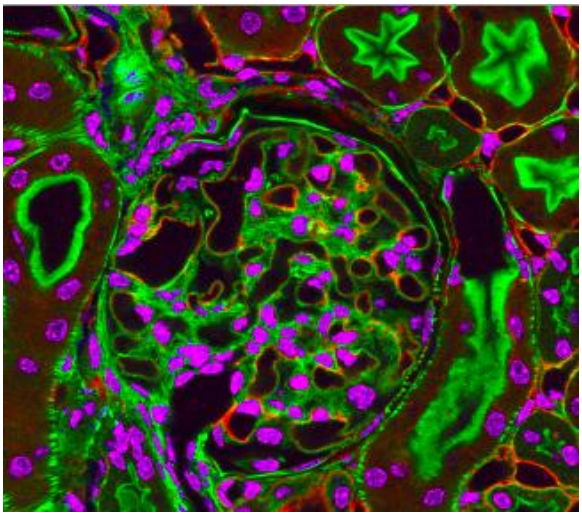

Figure 35. Photograph of kidney tissue taken using fluorescent light microscopy. Credit: NIGMS.

Understanding Prevalence, Risk Factors, and Underlying Biology

NIH-funded scientists have developed a new imaging technique that allows them to see deep into the kidney's internal structures and gain novel insights about cisplatin-induced chronic kidney disease in mice. A specialized imaging technique, called multiphoton microscopy, was previously limited because it

[755] Ciolino JB, et al. *Biomaterials* 2014;35(1):432-9. PMID: 24094935.
[756] https://nei.nih.gov/news/briefs/nei-human-gene-therapy-trial-retinoschisis-underway.
[757] https://www.niddk.nih.gov/health-information/kidney-disease.
[758] https://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf.

only gave a shallow view of the kidney. In this study, researchers applied a novel technique—using a "clearing" solution that replaced the water in the tissue with other chemicals, greatly increasing the imaging depth—to process samples of kidney tissue before looking at them under the microscope. This new imaging approach could provide novel insights about kidney damage caused by cisplatin and identify potential targets to make the drug safer for people; it could also be used to study other forms of kidney damage.[759]

Funded in 2015, the (Re)Building a Kidney Consortium aims to optimize approaches for the isolation, expansion, and differentiation of appropriate kidney cell types and their integration into complex structures that replicate human kidney function. These approaches are critical to the development of strategies for the de novo repair and regeneration of nephrons (the structural and functional units of the kidney) and the in vitro engineering of a biological kidney.[760,761,762]

Approximately 350,000 people in the U.S. with end-stage renal (kidney) disease rely on maintenance hemodialysis treatment, and many of these patients succumb to conditions resulting in part from chronic inflammation. NIAID-funded investigators showed that inhibiting specific components of the complement activation pathway during hemodialysis results in higher levels of anti-inflammatory molecules and could be a potential treatment option for reducing chronic inflammation in these patients.[763]

NIDDK-funded scientists discovered that depletion of a subset of cells in the developing mouse kidney resulted in fewer nephrons, a deficit that persisted throughout life. This study provides important information regarding one of the factors that contributes to the kidney's ability to remove waste. A fuller understanding of kidney development may provide clues as to possible strategies for growing new nephrons, which could help restore lost function.[764] Another NIDDK-funded study in mice looked at how damage to the kidney's proximal tubules, part of the kidney's duct system, is repaired after injury. After acute injury in the kidney, cells may be damaged and less able to filter blood, and some die. New cells in the proximal tubule appear to replace the impaired cells and restore the tubules' function; however, the origin of these new cells has been the topic of much debate. The researchers used sophisticated cell-labeling techniques to show that repair following acute kidney injury occurs through a return of mature proximal tubule cells to a somewhat more stem cell–like state, after which they proliferate.[765]

In another NIDDK-supported study, researchers found that direct interaction between chloride and the enzyme WNK1 plays an important role in the kidneys' regulation of salt levels and blood pressure. A

[759] Torres R, et al. *J Am Soc Nephrol* 2016;27(4):1102-12. PMID: 26303068.
[760] http://www.rebuildingakidney.org/.
[761] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-009.html.
[762] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-010.html.
[763] Reis ES, et al. *Immunobiology* 2015;220(4):476-82. PMID: 25468722.
[764] Cebrian C, et al. *Cell Rep* 2014;7(1):127-37. PMID: 24656820.
[765] Kusaba T, et al. *Proc Natl Acad Sci* 2014;111(4):1527-32. PMID: 24127583.

better understanding of WNKs' role in salt metabolism may allow for the development of new targeted treatment strategies for hypertension and other diseases.[766]

Using genome-wide screening techniques, researchers have found six new regions in the human genome that increase susceptibility to immunoglobulin A nephropathy (IgAN), a major cause of kidney failure worldwide. Using genome-wide screening, the scientists identified genes in people of Asian and European descent that affect both the risk of developing IgAN and the age at which the disease develops. These genetic regions are also associated with the risk of developing IBD. This observation suggests that IgAN may be a part of a group of autoimmune and inflammatory disorders that share some risk genes.[767]

A fraction of children and adolescents enrolled in the Chronic Kidney Disease in Children Study (CKiD), a study of more than 500 pediatric patients with mild to moderate kidney disease, have been found to have changes in their genetic material that may be important in the development of kidney disease and its complications. A better understanding of potential genetic variation–related causes of kidney disease in children, especially when there is no other identifiable cause, could pave the way to earlier interventions to preserve kidney function and better monitoring and treatments for associated conditions.[768] CKiD is also investigating risk factors for further reduction in kidney function, risk factors for heart disease, and long-term effects of poor growth in those with impaired kidney function, and is closely monitoring participants' brain development.[769]

NIDDK continued to support the Chronic Renal Insufficiency Cohort (CRIC) Study,[770] co-sponsored by NHLBI, to evaluate the long-term cardiovascular risk and outcomes of more than 3,700 people with chronic kidney disease.

Researchers have discovered that GLI proteins can promote kidney fibrosis—the growth of large amounts of collagen-rich connective tissue that can lead to organ damage—in mice and that inhibiting these proteins can reduce kidney damage. The scientists found that GLI proteins contribute to kidney fibrosis through their control of myofibroblasts' replication. Although more research is needed to confirm that GLI proteins work the same in humans as they do in mice, these findings suggest that the proteins might be promising targets for kidney fibrosis treatments.[771]

An NIDDK-supported study showed that people donate one of their kidneys to someone with kidney failure remain relatively healthy three years after donation. Researchers examined the health status, including tests of kidney function and blood pressure, of kidney donors (who, after their donation, have only one kidney) and non-donors (people with two kidneys) and found that these measures were similar

[766] Piala AT, et al. *Sci Signal* 2014;7(324):ra41. PMID: 24803536.
[767] Kiryluk K, et al. *Nat Genet* 2014;46(11):1187-96. PMID: 25305756.
[768] Verbitsky M, et al. *J Clin Invest* 2015;125(5):2171-8. PMID: 25893603.
[769] http://statepi.jhsph.edu/ckid/.
[770] http://www.cristudy.org/.
[771] Kramann R, et al. *J Clin Invest* 2015;125(8):2935-51. PMID: 26193634.

between the groups over the course of three years. Future studies could determine longer-term health outcomes for kidney donors.[772]

Using data from EHRs, NIAMS-funded researchers compared 136,529 patients with moderate psoriasis and 7,354 patients with severe psoriasis to 689,702 unaffected patients to assess whether the psoriasis patients were more likely to develop chronic kidney disease. Results showed that moderate to severe psoriasis is associated with an increased risk of chronic kidney disease. Additional studies are needed to confirm these results, understand the biological mechanisms that link psoriasis to kidney disease, and investigate the effect of various treatments for psoriasis on kidney disease risk. In light of these findings, closer monitoring of patients with moderate to severe psoriasis for signs of kidney disease may be warranted.[773]

An NIDDK-supported study found that the levels in urine of genetic material from podocytes, a type of kidney cell, correlate with loss of kidney function. These findings support the hypothesis that podocyte depletion is an important element of some forms of progressive kidney disease. Furthermore, measurement of urine levels of podocyte-derived genetic material may provide an easy, nonintrusive way to evaluate and monitor podocyte health in people with glomerular diseases.[774]

Improving Treatment and Prevention

Established in 2000, NIDDK's National Kidney Disease Education Program[775] (NKDEP) aims to improve early detection of chronic kidney disease (CKD), facilitate identification of patients at greatest risk for progression to kidney failure, promote evidence-based interventions to slow progression of CKD, and support the coordination of federal responses to CKD. In addition to providing a broad range of educational brochures and fact sheets, NKDEP develops resources to help health care providers and educators present kidney health information to the public. In 2015, NKDEP's newest resources have included training programs for diabetes educators, community health workers, and pharmacists, as well as a guide for primary care clinicians.

Researchers have used an animal model to show that a medical machine called a lithotripter may improve treatment of kidney stones. Lithotripters generate shock waves that pass through a person's body to break a kidney stone into smaller pieces, but the NIDDK-supported study found that more powerful lithotripters shift the shock wave off-target, making the wave less efficient. Introducing a groove around the outer portion of the lens redirected the shock wave to its proper target in an animal model. If future research shows similar benefits in people with kidney stones, this newly designed lens could improve the lithotripters used in medical practice.[776]

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[772] Kasiske BL, et al. *Am J Kidney Dis* 2015;66(1):114-24. PMID: 25795073.
[773] Wan J, et al. *BMJ* 2013;347:f5961. PMID: 24129480.
[774] Wickman L, et al. *J Am Soc Nephrol* 2013;24(12):2081-95. PMID: 24052633.
[775] http://www.nkdep.nih.gov.
[776] Neisius A, et al. *Proc Natl Acad Sci* 2014;111(13):E1167-75. PMID: 24639497.

In FY 2014, NIDDK created a multidisciplinary consortium to promote translational research that focuses on the development and validation of targeting probes, imaging technologies, or biomarkers to detect and measure pathologic fibrosis for molecular classification, risk stratification, and/or morphology as a step toward prevention or treatment. Studies will be restricted to pathological fibrosis due to congenital or acquired processes caused by acute or chronic injury to the kidneys, prostate, urinary tract, or bone marrow. The consortium's projects include studies to develop noninvasive MRI methods for assessing kidney fibrosis and to identify and validate novel serum and urine biomarkers of kidney fibrosis.[777]

Long-term use of trimethoprim and sulfamethoxazole can reduce the risk of recurrent urinary tract infections (UTIs) by up to 80 percent in children with vesicoureteral reflux. Further analysis from this NIDDK-supported clinical trial may provide insight into other factors that could reduce susceptibility to recurrent UTIs and kidney scarring.[778]

Two NIH-funded studies found that using two drugs was no more effective than using a single drug to slow disease progression in people with autosomal dominant polycystic kidney disease (ADPKD. Rigorous blood pressure treatment slowed growth of kidney cysts, a marker of ADPKD, but had little effect on kidney function compared with standard blood pressure treatment.[779,780]

In FY 2015, NLM and NIDDK researchers collaborated to identify strategies for using EHRs to better manage chronic kidney disease and extrapolated the lessons learned as a model for improving chronic disease care.[781]

Mental Health

Mental illnesses affect millions of Americans each year, affecting people of all ages, sexes, ethnic, racial, and socioeconomic groups. Depression is the most prevalent mental illness, affecting more than 26 percent of Americans.[782] In addition, numerous other forms of chronic mental illnesses cause suffering among Americans, including anxiety, eating disorders, and bipolar disorder, to name a few. Anxiety, for example, affects 15 percent of Americans over the course of their lifetime.[783]

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

[777] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-026.html.
[778] RIVUR Trial Investigators, et al. *N Engl J Med* 2014;370(25):2367-76. PMID: 24795142.
[779] Schrier RW, et al. *N Engl J Med* 2014;371(24):2255-66. PMID: 25399733.
[780] Torres VE, et al. *N Engl J Med* 2014;371(24):2267-76. PMID: 25399731.
[781] Drawz PE, et al. *Clin J Am Soc Nephrol* 2015;10(8):1488-99. PMID: 26111857.
[782] https://www.cdc.gov/mentalhealth/basics.htm.
[783] https://www.cdc.gov/mentalhealth/basics/burden.htm.

was 10.1 years, relative the life expectancy of the general population.[784] NIH seeks to invest in research to understand, prevent, and treat chronic mental illnesses.

Understanding Prevalence, Risk Factors, and Underlying Biology

To better understand the causes of depression in adolescents, NICHD-supported researchers analyzed data from approximately 16,000 adolescents in grades 7–12 in the 1994–95 school years. The results showed that schools were notably more relevant than neighborhoods for adolescent depression, even after the researchers took race, ethnicity, and socioeconomic status into account. The results suggest that intervention programs directed at schools may be especially helpful in addressing depression among young people.[785]

NIMH and the U.S. Army partnered with four universities to carry out the largest study of suicide risk and resilience ever conducted among military personnel. In 2014 and 2015, more than 20 publications emerged from this study, including results showing that soldiers who are diagnosed with mental illnesses are at increased of suicide risk after leaving a hospital setting. This finding could be an important clue toward better prevention of suicide among military populations.[786,787,788,789,790,791]

Although life expectancy has increased in the U.S., mortality rates vary across racial, ethnic, and socioeconomic groups. Mental illnesses are frequently associated with a variety of other comorbid disorders. Among a national sample of adults age 30 or older who participated in the National Health and Nutrition Examination Survey (NHANES, 2005 and 2007), the relationship between diabetes status and depression and antidepressant use depends on whether the diabetes has been clinically identified. Clinically identified diabetes was associated with 4.3-fold greater odds of depression, but undiagnosed diabetes was not significantly associated with depression. Clinically identified diabetes was also associated with 1.8-fold greater odds of antidepressant use, but undiagnosed diabetes was not significantly associated with antidepressant use.[792] These findings are consistent with the hypothesis that the relationship between diabetes and depression may be attributable to factors related to disease management.[793]

NIMH- and NINDS-supported investigators demonstrated how a rare mutation in a suspect gene labeled Disrupted in Schizophrenia-1 (*DISC1*) disrupts the activation and deactivation of dozens of other genes that support connections between neurons. Researchers used iPSC techniques to differentiate patients' skin cells are into neurons and are then studied the cells in a petri dish. Researchers found abnormal

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[784] Walker ER, et al. *JAMA Psychiatry.* 2015;72(4):334-41. PMID: 25671328.
[785] Dunn EC, et al. *Am J Public Health* 2015;105(4):732-40. PMID: 25713969.
[786] Nock MK, et al. *JAMA Psychiatry* 2014;71(5):514-22. PMID: 24590178.
[787] Ursano RJ, et al. *Psychiatry* 2014;77(2):107-19. PMID: 24865195.
[788] Kessler RC, et al. *JAMA Psychiatry* 2014;71(5):504-13. PMID: 24590120.
[789] Schoenbaum M, et al. *JAMA Psychiatry* 2014;71(5):493-503. PMID: 24590048.
[790] http://www.nimh.nih.gov/news/science-news/2014/soldiers-at-increased-suicide-risk-after-leaving-hospital.shtml.
[791] http://www.armystarrs.org/.
[792] Mezuk B, et al. *Health Psychol* 2013;32(3):254-63. PMID: 23437855
[793] https://projectreporter.nih.gov/project_info_description.cfm?aid=8729896&icde=34700000.

expression of the protein made by *DISC1* and discovered *DISC1's* role as a hub that regulates expression of many genes implicated in mental disorders.[794,795] The results suggest a common disease mechanism underlying major mental illnesses that integrates genetic risk, aberrant neurodevelopment, and synapse dysfunction. The overall approach may hold promise for testing potential treatments to correct synaptic deficits.

NIMH funds the Schizophrenia Working Group of the Psychiatric Genomic Consortium, which reported on the largest genomic study of any psychiatric disorder at the time of publication. This study combined data from all available schizophrenia genetic samples to search for clues to the molecular basis of the disorder. Researchers discovered inherited variations in the genetic code that were linked to schizophrenia, 83 of which had not been previously reported. The newfound genomic signals are not simply random sites of variation; instead, they converge around pathways underlying the workings of processes involved in schizophrenia, such as communication between brain cells, learning and memory, cellular ion channels, immune function, and a key medication target.[796,797,798] These results highlight genetic programming's role in the risk architecture of schizophrenia and validate the strategy of applying genomic analyses to understand this complex disorder.

Improving Treatment and Prevention

NIMH funded the Fast-Fail Trials (FAST) initiative through three contracts to provide a rapid way to test new or repurposed compounds for their potential as psychiatric medications. The three FAST teams of researchers are focused on different mental disorders: Psychotic Spectrum Disorders (FAST-PS); Autism Spectrum Disorders (FAST-AS); and Mood and Anxiety Spectrum Disorders (FAST-MAS).[799]

Clinical trials have shown that the anesthetic drug ketamine can lift depression much faster than the most commonly used antidepressant medications, which often require weeks to take effect. However, although there are legitimate medical uses, ketamine also has dissociative, euphoric, and addictive properties, making it a potential drug of abuse and limiting its usefulness as a depression medication. But a team of intramural researchers and grantees found that a chemical byproduct, or metabolite, of ketamine is likely responsible for its antidepressant properties and that the metabolite works without triggering any of the unwanted side effects associated with ketamine itself. This finding is the result of in-depth collaboration between intramural researchers at NIMH, NIA, and NCATS, along with academic researchers.[800]

In addition to supporting this research on ketamine and its metabolites, NIMH is funding Rapidly-Acting Treatments for Treatment-Resistant Depression (RAPID), an ongoing project that promotes

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[794] Wen Z, et al. *Nature* 2014;515(7527):414-8. PMID: 25132547.
[795] http://www.nimh.nih.gov/news/science-news/2014/suspect-gene-corrupts-neural-connections.shtml.
[796] Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* 2014;511(7510):421-7. PMID: 25056061.
[797] http://www.nimh.nih.gov/news/science-news/2014/schizophrenias-genetic-skyline-rising.shtml.
[798] https://www.med.unc.edu/pgc.
[799] http://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml.
[800] https://www.nia.nih.gov/newsroom/2016/05/ketamine-lifts-depression-byproduct-its-metabolism.

development of speedier therapies for severe, treatment-resistant depression. The project supports a team of Massachusetts General Hospital researchers who are developing promising pharmacological and non-pharmacological treatments that lift depression within a few days.[801]

Depression during pregnancy is associated with poor birth outcomes for both mother and infant and is also a risk factor for postpartum depression, which can increase a woman's lifetime risk of this potentially devastating disorder. A physiological biomarker of depression for which a woman could be tested would be an important advance, because subtle psychological symptoms of early depression may not be recognized. Since the naturally occurring substance, brain-derived neurotrophic factor (BDNF), is under study as an early indicator of postpartum depression (as well as certain other illnesses), NICHD scientists measured its levels in a large sample of women early in pregnancy and also administered a depression screening interview. The researchers found lower BDNF levels in the pregnant women whose interview scores indicated depression. Although further research is needed, this finding suggests that BDNF could be a helpful early biomarker of depression during pregnancy.[802]

NIMH, OBSSR, and the National Institute of Justice are collaborating on a four-year, $6.8 million study to address a critical gap in evidence-based suicide prevention, with a focus on high-risk individuals who are transitioning from jail to community settings. This study, Suicide Prevention for at-Risk Individuals in Transition (SPIRIT), uses the jail setting as an opportunity to prevent suicide among high-risk individuals as they return to the community. SPIRIT is NIMH's largest investment in suicide prevention in the justice system.[803]

FIC supports research and research training on chronic, noncommunicable diseases and disorders, with the ultimate goal of implementing evidence-based interventions relevant to low- and middle-income countries. One grantee has demonstrated how various online media platforms and newspapers affect the rates of suicide by inhaling carbon monoxide produced by charcoal burning (CB) in mainland China.[804] A content analysis of the incidence of reported CB and online searches using CB-related keywords showed that two-thirds of the web links provided detailed information, and 15 percent of those sites had pro-suicide attitudes, most not offering significant encouragement to seek help. This research highlights the importance of media in behavioral outcomes and suicide prevention.[805]

CDC reported that in 2014, suicide was the second leading cause of death for young people ages 10–24.[806] In recent years, NIMH has focused on hospital emergency departments as a prime setting for suicide prevention efforts; in 2014, it funded the Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) study, launched in a network of hospital emergency departments across the country.

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[801] http://www.nimh.nih.gov/research-priorities/research-initiatives/rapidly-acting-treatments-for-treatment-resistant-depression-rapid.shtml.
[802] Fung J, et al. *BMC Psychiatry* 2015;15:43. PMID: 25886523.
[803] http://www.nimh.nih.gov/news/science-news/2015/embracing-the-spirit-of-reducing-suicide.shtml.
[804] https://projectreporter.nih.gov/project_info_description.cfm?aid=8901338&icde=34700085.
[805] Cheng Q, et al. *PLoS One* 2015;10(10):e0140686. PMID: 26474297.
[806] https://www.cdc.gov/injury/images/lc-charts/leading_causes_of_death_age_group_2014_1050w760h.gif.

ED-STARS will develop and test a personalized, computer-based suicide risk screening tool for teenagers.[807]

For years, doctors have prescribed lithium to treat adults with bipolar disorder, a brain disorder marked by extreme mood swings. However, until recently lithium had not been tested in children, although some doctors did prescribe the drug for children with bipolar disorder. In a new study, NIH scientists have confirmed that lithium is an appropriate treatment for children diagnosed with the form of the disorder known as bipolar type 1.[808]

NIMH funded the Recovery After an Initial Schizophrenia Episode (RAISE) program, a large-scale research initiative that examined NAVIGATE and the Connection Program, two coordinated specialty care treatments for people experiencing first-episode psychosis. One initiative that sprang from RAISE's efforts is OnTrackNY, a coordinated specialty care program for first-episode psychosis in New York. [809] During FY 2014 and 2015, the RAISE study resulted in several publications, including one focused on results from the NAVIGATE program and one on the Connection Program.[810,811,812]

Dissemination of knowledge gained through research is a key part of addressing mental health concerns, so NIMH has engaged in numerous efforts to share important research findings. For example, NIMH launched the RAISE website, which provides NIMH-developed and curated educational resources for patients, families, and state health administrators.[813] NIMH also hosted live social media Q&A sessions on a variety of mental health topics. In FY 2014 and 2015, NIMH engaged experts from across NIH to discuss a range of topics, including perimenopausal depression, cancer and psycho-oncology, pediatric bipolar disorder, and depression and novel medicines. The sessions were widely attended, allowing NIH experts to engage with millions of people on NIMH's social media channels, including Twitter, Facebook, and Google+.[814,815,816] In addition, NIMH and NICHD partnered with the Delta Sigma Theta (DST) Sorority, Inc. to launch the Mental Health Across the Lifespan initiative. The initiative seeks to raise awareness about mental health issues affecting women and their families throughout the lifespan, including mental disorders such as postpartum depression, and issues that can affect mental health, including bullying and aging.[817]

Understanding barriers to access and utilization of mental health care is another important aspect of the federal efforts to improve mental health. An NIMHD-funded study is prospectively assessing the contributions that health literacy, health insurance literacy, mental health stigma, discrimination, and trust (or mistrust) of the health system make to primary care utilization over the course of six months

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[807] http://www.nimh.nih.gov/news/science-news/2014/personalized-screen-to-id-suicidal-teens-in-14-ers.shtml.
[808] Findling RL, et al. *Pediatrics* 2015;136(5):885-94. PMID: 26459650.
[809] https://www.nimh.nih.gov/news/science-news/2015/psychosis-treatment-program-expands-in-new-york.shtml.
[810] Mueser KT, et al. *Psychiatr Serv* 2015;66(7):680-90. PMID: 25772766.
[811] Dixon LB, et al. *Psychiatr Serv* 2015;66(7):691-8. PMID: 25772764.
[812] http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml.
[813] http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml.
[814] http://www.nimh.nih.gov/health/twitter-chats/index.shtml.
[815] https://www.facebook.com/nimhgov.
[816] https://plus.google.com/+NIMHgov.
[817] http://www.nimh.nih.gov/health/educational-resources/the-mental-health-across-the-lifespan-initiative.shtml.

among a racially diverse sample of mental health center patients with serious mental illness in an urban community.[818]

Musculoskeletal and Skin Diseases

There are many different types of musculoskeletal and skin diseases, affecting millions of Americans. For example, 16 percent of women over age 50 have osteoporosis in the neck or spine.[819] Psoriasis, a chronic autoimmune skin disease, affects more than 3.1 million Americans.[820] Musculoskeletal and skin diseases often occur as complications from other conditions, compounding the impact on a person's quality of life and health. NIH, led by NIAMS, 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—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, NIAMS, NICHD, NINDS, and NHLBI support a total of six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. The centers promote collaborative basic, translational, and clinical research and provide important resources that can be used by the national muscular dystrophy research community. The centers also provide outstanding environments for the training of new scientists, and center investigators are expected to participate in community outreach efforts with the patient and advocacy communities. The most recent awards were issued in FY 2015.[821] More information on these centers is available in Chapter 4.

Understanding Prevalence, Risk Factors, and Underlying Biology

With funding from NIH, the Center for the Advancement of Science in Space, and the National Aeronautics and Space Administration (NASA) Kennedy Space Center, a team of investigators has developed tools that researchers on Earth and in space are using to understand how bones respond to stresses like weight-bearing exercises and gravity, as well as how these processes break down during unloading conditions like prolonged bed rest or space travel. New findings from a ground-based component of the study are unpacking the complex relationship between gene expression and hormones that influence cell behavior. In spring 2015, the experiments moved to the International Space Station, so that the microgravity results can be compared with other observations about bone cell behavior on Earth.[822,823]

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[818] https://projectreporter.nih.gov/project_info_description.cfm?aid=8994609&icde=34702313.
[819] https://www.cdc.gov/nchs/fastats/osteoporosis.htm.
[820] https://www.niams.nih.gov/Health_Info/Psoriasis/default.asp.
[821] https://www.wellstonemdcenters.nih.gov/.
[822] Spatz JM, et al. *J Biol Chem* 2015;290(27):16744-58. PMID: 25953900.
[823] http://www.nasa.gov/mission_pages/station/research/news/osteocytes.

A NIAMS- and NIA-funded study on osteoporotic fractures found that bone mineral density (BMD) is closely related to fracture risk. The findings, published in 2012, contributed to Medicare's decision to pay for BMD measurements of numerous older Americans.[824] Many Americans started taking bone-preserving drugs due to the results of these tests, and the rate of hip fractures among female beneficiaries has since dropped nearly 25 percent. New findings from this and other studies are suggesting ways to refine the screening guidance. Women at the highest risk of osteoporosis might benefit from annual exams, while women with the lowest risk could be tested much less frequently, unless other aspects of their health change. Similarly, postmenopausal women ages 50–64 without osteoporosis on their first BMD test are unlikely to benefit from frequent rescreening before age 65.[825,826]

Osteomalacia, softening of the bones due to reduced mineralization, is associated with a number of diseases, including fibrous dysplasia of bone, which is caused by overproduction of the phosphate-regulating hormone FGF23. NIDCR intramural researchers identified genetic mutations that activate Ras, a signaling protein, in bone, the endogenous source of FGF23.[827] This discovery provides the first evidence that elevated FGF23 levels in serum, low phosphate levels, and osteomalacia are associated with abnormal Ras activation, and the finding may provide new insights into the regulation of FGF23.

Two groups of NIAMS-supported investigators demonstrated that dysregulation of certain proteins involved in inflammation impairs muscle tissue regeneration. The two independent publications suggest that during aging and in the dystrophies, chronic inflammation activates the JAK-STAT signaling pathway, which facilitates gene expression, in an unregulated manner that impairs regeneration of damaged tissue. The researchers also showed that interfering with this pathway may be a way to treat muscle wasting and disease. This finding is particularly encouraging because JAK-STAT inhibitors are FDA-approved for other conditions.[828,829]

Improving Treatment and Prevention

Repairing large gaps in bone is very challenging. Surgeons often try to fill the space between bone fragments with bone taken from other sites in the patient's body (autografts) or bone taken from deceased donors (allografts), but limited tissue supplies and, in the case of autografts, pain at the original site of the transplanted tissue make both these approaches less than ideal. To improve the healing capability of allografts, one research group wrapped broken bones in mice with an artificial membrane containing a combination of early stage stem cells, called mesenchymal stem cells (MSCs), and stem cells that have committed to forming bone (osteoprogenitor cells). A 50-50 mixture of the two

[824] Gourlay ML, et al. *N Engl J Med* 2012;366(3):225-33. PMID: 22256806.
[825] Berry SD, et al. *JAMA* 2013;310(12):1256-62. PMID: 24065012.
[826] Gourlay ML, et al. *Menopause* 2015;22(6):589-97. PMID: 25349960.
[827] Lim YH, et al. *Hum Mol Genet* 2014;23(2):397-407. PMID: 24006476.
[828] Tierney MT, et al. *Nat Med* 2014;20(10):1182-6. PMID: 25194572.
[829] Price FD, et al. *Nat Med* 2014;20(10):1174-81. PMID: 25194569.

cell types showed increased bone formation and a higher formation rate, better graft–host integration, and improved biomechanics than those of MSCs and osteoprogenitor cells alone.[830]

A group of NIAMS-funded investigators searching for a better way to repair anterior cruciate ligament (ACL) injuries that frequently affect athletes found that stitching a bioengineered sponge between the torn ends of an injured ACL allows blood to clot and collect around the damaged ligament. Because blood naturally contains stem cells and growth factors, the blood-soaked sponge acts as a "bridge" that encourages ACL healing. Studies in large animals showed that the bioengineered sponge was much less likely to lead to arthritis and that it healed ACL injuries as well as standard reconstruction surgery. In November 2014, FDA approved first-in-human safety testing of the sponge in 10 people with ACL injuries.[831,832]

There are many risks and complications associated with type 2 diabetes, including bone fractures that cannot be predicted with conventional dual-energy X-ray absorptiometry (DXA) measurements. Researchers tested a relatively noninvasive technique called microindentation, which estimates density by measuring how far a tiny needle can penetrate bone, and found that the approach detected lower bone material strength (BMS) in patients with type 2 diabetes than in people without diabetes. The research also found that lower BMS was correlated with higher blood levels of glycated hemoglobin (i.e., hemoglobin A1c, a biomarker of blood glucose levels) over the last decade. This study not only makes progress toward developing a tool that could be used to predict fracture risk of people who have type 2 diabetes, it also illustrates a relationship between bone strength and blood sugar, and it suggests that people with more severe and less adequately treated diabetes may be at a greater risk of bone fracture than those whose disease is well controlled.[833]

While fragility fractures are the hallmark of osteoporosis and are associated with severely low bone mineral density (BMD), a large percentage of fractures occur in women with BMD that is low but does not meet the threshold to be classified as osteoporosis. Using high-resolution peripheral quantitative computed tomography (HR-pQCT) and mathematical modeling to analyze bones in the distal radius of the arm and the distal tibia of the leg of women with low (but not osteoporotic) BMD, researchers determined that women in the fracture group had fewer plate-like structures and fewer connections between rod-like structures in their arm bones than women with similar BMD measurements but no a history of fractures did. Two-dimensional DXA evaluation is an appropriate screening method for overall fracture risk in the general population. However, it may be necessary to further test women who have fractures or a high risk of fracturing, as identified by other means, with a tool like HR-pQCT before treatment options are selected.[834]

A 2015 finding from researchers funded by NIAMS, NICHD, and NCATS describes the identification of 44 proteins that could potentially serve as biomarkers for Duchenne muscular dystrophy (DMD) because

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[830] Hoffman MD, et al. *Biomaterials* 2015;52:426-40. PMID: 25818449.
[831] Murray MM, et al. *Am J Sports Med* 2013;41(8):1762-70. PMID: 23857883.
[832] http://vector.childrenshospital.org/2013/09/acl-repair-a-game-changer/.
[833] Farr JN, et al. *J Bone Miner Res* 2014;29(4):787-95. PMID: 24123088.
[834] Stein EM, et al. *J Bone Miner Res* 2014;29(5):1101-9. PMID: 24877245.

they are present in significantly different amounts between patients with DMD and age-matched controls. The lack of DMD biomarkers for monitoring disease progression and response to therapy has been a major impediment to advancing new treatments, and the proteins identified from this study may fill that gap. Furthermore, the specific patterns also provide insight into how the disease progresses. For example, levels of some proteins were more abundant than normal in younger patients but fell as the boys got older, suggesting that the molecules were involved in the early stages of muscle deterioration and might be appropriate therapeutic targets.[835]

NIDCR IRP researchers have also made advances in treating fibrous dysplasia, a crippling bone disease, with a drug called alendronate, which is normally used to treat osteoporosis. Treatment with a alendronate led to a reduction in markers of bone turnover and to improvement in bone mineral density.[836]

NIH is committed to providing support that allows clinical research groups to access additional resources beyond NIH. For example, NIAMS awarded a two-year grant to a team of scientists to plan a clinical trial in DMD. Thanks to the NIAMS-funded planning efforts, a pharmaceutical company assumed responsibility for funding the randomized, double-blinded, placebo-controlled, Phase II clinical trial, the largest trial yet conducted in boys with this disease. Recruitment is complete, and the study should be finished in April 2018.[837]

Obesity

More than one-third of U.S. adults (36.5 percent) are obese,[838] and around 17 percent of children and adolescents suffer from obesity,[839] 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, including heart disease, stroke, type 2 diabetes, and some forms of cancer. Further, obesity is estimated to cost the U.S. more than $147 billion in annual medical spending.[840] 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

Between 1999 and 2012, the prevalence of obesity in children ages 2 to 19 rose in all demographic categories, according to an NICHD-supported analysis of NHANES. There was no significant change in the overall rate of obesity prevalence from 2010 to 2012, suggesting that the overall rate of childhood

[835] Hathout Y, et al. *Proc Natl Acad Sci* 2015;112(23):7153-8. PMID: 26039989.
[836] Boyce AM, et al. *J Clin Endocrinol Metab* 2014;99(11):4133-40. PMID: 25033066.
[837] https://clinicaltrials.gov/ct2/show/NCT01865084.
[838] https://www.cdc.gov/obesity/data/adult.html.
[839] https://www.cdc.gov/obesity/data/childhood.html.
[840] https://www.cdc.gov/obesity/data/adult.html

obesity in the U.S. may be stabilizing. But there was a notable upward trend in severe and extreme obesity, particularly in older children, adolescents, and non-Hispanic Black and Hispanic children.[841]

Researchers funded by NIDDK have identified biological pathways that induce the formation of calorie-burning fat cells, called beige fat cells, within the body's white adipose (fat) tissue, which is the more abundant type of fat tissue known for storing calories. In research linking exercise to beneficial effects from the "browning" of white fat, scientists found that in mice and humans, muscle produces a molecule called meteorin-like following exercise. Experiments in mice showed that meteorin-like activates beige fat cells within white fat tissue and is associated with improved health; it is also induced by cold temperatures.[842] This and other NIDDK-funded studies have also identified cells and biological molecules in the immune system that are involved in the production of beige fat cells.[843,844] This research may lead to new strategies to increase calorie burning by promoting the activation of beige fat as a potential therapy for obesity and associated metabolic diseases.

NIDDK-funded scientists used state-of-the-art techniques to map a series of cells in different parts of the brain that relay signals to drive appetite in mice.[845] Future research could build on this finding to determine whether humans have a similar pathway of appetite regulation through these types of brain cells; if so, researchers could target it to develop obesity drugs that help people feel full after eating less food. Identifying the interaction between neurological effects and eating behaviors is an essential component to understanding and controlling obesity. The Neuronal and Behavioral Effects of Implicit Priming in Obese Individuals award, funded by NIDDK and OBBSR, encourages an exploratory clinical trial among obese individuals to study mechanisms that signal food intake and encourage changes in perception of food or appetite. Recent results identify implicit priming as a way to reduce the appeal of high-calorie foods.[846,847]

Analyses of data from nearly 122,000 deliveries has determined that maternal obesity, before or during pregnancy, is a significant risk factor for congenital heart defects in infants. The study was the first to disentangle the effects of maternal weight and maternal blood sugar levels (elevated blood glucose), which together had been identified as risk factors for a child's congenital heart problems. The new data highlight the importance of weight management for women who are or are planning to become pregnant.[848] The HAPO FUS, cosponsored by NIDDK and NICHD, is determining whether maternal glucose levels during pregnancy are associated with later obesity or adverse metabolic or cardiovascular status in children of mothers with well-characterized pregnancies; it is also looking at maternal outcomes.[849]

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[841] Skinner AC, et al. *JAMA Pediatr* 2014;168(6):561-6. PMID: 24710576.
[842] Rao RR, et al. *Cell* 2014;157(6):1279-91. PMID: 24906147.
[843] Brestoff JR, et al. *Nature* 2015;519(7542):242-6. PMID: 25533952.
[844] Lee MW, et al. Cell 2015;160(1-2):74-87. PMID 25543153.
[845] Garfield AS, et al. *Nat Neurosci* 2015;18(6):863-71. PMID: 25915476.
[846] https://projectreporter.nih.gov/project_info_description.cfm?aid=8915165&icde=34704271.
[847] Legget KT, et al. *Am J Clin Nutr* 2015;102(2):249-55. PMID: 26109580.
[848] Brite J, et al. *Int J Obes (Lond)* 2014;38(6):878-82. PMID: 24362506.
[849] https://www.niddkrepository.org/studies/hapo-fus/.

A comparison of how preadolescent children performed certain tasks found that children who were obese were slower and less accurate in completing the tasks and slower to recognize and fix their errors, compared with children with healthy weights. The study of the children's cognitive control—the ability of individuals to monitor their thoughts and actions—included electronic monitoring of brain waves. NICHD-supported researchers found that the part of the brain that detects errors was larger and more responsive in the healthy weight children, compared with those who were obese. It remains to be determined, however, whether obesity causes decreases in cognitive control whether decreased cognitive control may lead to obesity.[850]

Data from a new NIDCD-supported study suggest that approximately 30 percent of the variation in sweetness perception is determined by genetic factors. This finding calls into question the popular belief that some people eat too much sugar because they were raised on a high-sugar diet. Instead, individuals who inherit a weak ability to perceive sweet flavors may need more sugar to reach their desired level of sweetness than those who inherit a different set of genes do.

With data from hundreds of thousands of people, NIDDK-funded scientists studying obesity discovered variants in many human genomic regions associated with body mass index (BMI, a measure of weight relative to height) and many other regions that influence body fat distribution—whether extra calories are likely to be stored as abdominal fat, which is generally more detrimental, or at the hips. Future research to identify the genes involved may yield new targets for precision medicine.[851,852]

The internal environment also is believed to play a role in obesity. NIDDK-funded researchers are discovering how the trillions of bacteria and other microbes in the intestines (known as gut microbes or the gut microbiome) may play a role in obesity. For example, in a study in mice, scientists found that the composition of different types of gut bacteria in the mice was affected by genetic background (whether the mice were more or less prone to obesity), diet (whether high-fat or normal mouse chow), and the environments in which the mice were bred. By doing bacterial transplant experiments in the mice, the researchers found that some types of gut bacteria conferred better metabolic health than others.[853] Additionally, NIDDK-funded scientists studying human twins, some lean and some obese, showed that genetic factors help shape the gut microbiome and that some of these bacteria, when transplanted into mice, could affect mouse body weight.[854] These results suggest that developing strategies to modify the gut microbiome may lead to future therapies to improve weight and metabolic health. Additional updates on NIH gut microbiome research are included in the Microbiome section of this chapter.

A range of lifestyle factors may also affect obesity. An NHLBI-funded multinational study has provided new evidence that short sleep duration is associated with obesity. Researchers analyzed sleep and dietary data from 15,000 adults who enrolled in several cohort studies and found that longer sleep

[850] Kamijo K, et al. *Cereb Cortex* 2014;24(3):654-62. PMID: 23146965.
[851] Locke AE, et al. *Nature* 2015;518(7538):197-206. PMID: 25673413.
[852] Shungin D, et al. *Nature* 2015;518(7538):187-96. PMID: 25673412.
[853] Ussar S, et al. *Cell Metab* 2015;22(3):516-30. PMID: 26299453.
[854] Goodrich JK, et al. *Cell* 2014;159(4):789-99. PMID: 25417156.

duration was associated with a lower intake of saturated fats in young adults and a lower intake of carbohydrates in older women.[855]

Obesity has been linked to increased risk for a range of other diseases. Research conducted as part of the NIEHS-funded Sister Study shows that waist circumference, a measure of central body fat, is independently and positively associated with both premenopausal and postmenopausal breast cancer risk.[856] Another NIEHS-funded study found that obesity, rather than diet, causes changes in the colon that may lead to colorectal cancer.[857] Further, NIEHS scientists discovered that female mice exposed to bisphenol A (BPA) during development and tested as adults showed less motivation to engage in voluntary physical activity and altered metabolism of carbohydrates versus fats.[858]

Improving Treatment and Prevention

NIEHS and NICHD conduct a joint grant program, the Role of Environmental Chemical Exposures in the Development of Obesity, Type 2 Diabetes, and Metabolic Syndrome, to support research on the role that environmental chemical exposures during development or other windows of sensitivity play in weight gain, altered glucose/insulin sensitivity, and altered lipid metabolism. The program has generated significant growth in this area of research and in the number of related publications. Between 2014 and 2015, NIEHS-funded researchers published nearly 80 papers on this topic.

Research in mice and humans suggests that restricting eating to fewer hours per day, during normal periods of activity, may help individuals achieve a healthier weight. NIDDK-funded researchers found that mice given 24-hour access to food gained more weight than mice with access only during their active phase; shorter periods of food access (e.g., 9 or 12 hours) led to healthier weights. Time-restricted feeding five days per week also improved weight, blood sugar, and body fat levels in the mice, compared with daily 24-hour food access.[859] In a study that used a smartphone app to monitor how people eat, NIDDK-funded researchers found that adults consume food and beverages frequently; over half of the participants consumed calories over a span of approximately 15 hours each day. The investigators have begun to explore whether limiting the times for daily calorie consumption (e.g., to 10-12 hours per day) could help people lose weight.[860]

NHLBI-funded investigators identified bile acid receptors as targets for a promising new approach to treat obesity and metabolic syndrome. This receptor lines the intestines and is activated after a meal. The investigators developed an oral compound called fexaramine that activates the receptor, tricking the body into reacting as if it has consumed calories and leading to weight loss in mice. However, human studies would need to be conducted to validate this new approach.[861]

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[855] Dashti HS, et al. *Am J Clin Nutr* 2015;101(1):135-43. PMID: 25527757.
[856] White AJ, et al. *Cancer* 2015;121(20):3700-8. PMID: 26193782.
[857] Li R, et al. *Cell Metab* 2014;19(4):702-11. PMID: 24703701.
[858] Johnson SA, et al. *J Dev Orig Health Dis* 2015;6(6):539-52. PMID: 26378919.
[859] Chaix A, et al. *Cell Metab* 2014;20(6):991-1005. PMID: 25470547.
[860] Gill S, et al. *Cell Metab* 2015;22(5):789-98. PMID: 26411343.
[861] Fang S, et al. *Nat Med* 2015;21(2):159-65. PMID: 25559344.

A conference sponsored by FIC was convened in FY 2014 to stimulate the sharing of lessons learned and the generation of new ideas on reversing the global obesity epidemic and its health effects among children. Topics discussed in the conference included emerging and critical research priorities, research capacity needs in LMICs, and the translation of evidence into obesity-related policy and programs. A subsequent journal supplement in *Obesity Reviews* was published in September 2017.[862]

COPE-Healthy Lifestyles TEEN, a teacher-delivered intervention program, seeks to promote healthy lifestyles and treat severe depression through improved health behaviors, lower body mass index, and improved social skills and academic performance in high school adolescents. Routine integration of such programs into health education curricula in high school settings may be an effective way to prevent high-risk teen populations from becoming overweight or obese and could lead to better physical health, psychosocial outcomes, and academic performance. This NINR-funded study was one of the first to report multiple immediate improvements sustained over time, using a teacher-delivered, cognitive-behavioral skills-building intervention program incorporated into a high school health education class.[863]

In multiple studies, NIDDK-funded researchers advanced knowledge of the effects of bariatric surgery as a treatment for people who have severe obesity or varying levels of obesity as well as type 2 diabetes. This information can help inform healthcare decisions and may lead to the development of new therapeutic strategies. In the Longitudinal Assessment of Bariatric Surgery (LABS) observational study of more than 2,000 adults with severe obesity who underwent bariatric surgery, researchers found substantial weight loss three years after surgery, although there were differences in the extent of weight loss between two different surgical procedures and variation in weight loss even among individuals who had had the same procedure. The study also found significant improvements in diabetes, blood pressure, and cholesterol[864] and reduced urinary incontinence.[865] Two small clinical trials found that after one year of treatment, bariatric surgery may be more effective than nonsurgical approaches for treating type 2 diabetes in adults who have mild or moderate levels of obesity.[866,867] An observational study of bariatric surgery in teens with severe obesity showed relatively few short-term complications 30 days after surgery; researchers have continued the Teen-LABS study to evaluate longer-term outcomes.[868]

NIDDK launched several new initiatives for research on bariatric surgery, a treatment that has become increasingly common in clinical practice for people who have severe obesity or lower levels of obesity along with serious obesity-related disease. Studies funded in FY 2015 that aim to use large datasets (e.g., from health care systems) to determine long-term risks/benefits of bariatric surgery could help inform treatment decisions; understand psychosocial and behavioral factors that may influence weight loss or regain after bariatric surgery, possibly leading to individualized health recommendations; and identify

[862] Caballero B, et al. *Obes Rev* 2017;18 Suppl 2:3-6. PMID: 28741905.
[863] Melnyk BM, et al. *J Sch Health* 2015;85(12):861-70. PMID: 26522175.
[864] Courcoulas AP, et al. *JAMA* 2013;310(22):2416-25. PMID: 24189773.
[865] Subak LL, et al. *JAMA Intern Med* 2015;175(8):1378-87. PMID: 26098620.
[866] Courcoulas AP, et al. *JAMA Surg* 2014;149(7):707-15. PMID: 24899268.
[867] Halperin F, et al. *JAMA Surg* 2014;149(7):716-26. PMID: 24899464.
[868] Inge TH, et al. *JAMA Pediatr* 2014;168(1):47-53. PMID: 24189578.

biologic mechanisms mediating weight loss and diabetes resolution after surgery, which could inform development of new non-surgical treatments.

NIDCD-supported scientists are trying to understand why one popular type of gastric bypass surgery (Roux-en-Y) not only causes weight loss but also changes an individual's taste preferences. After Roux-en-Y gastric bypass surgery, individuals often avoid sweet and fatty foods. The scientists theorize that surgery damages a part of the vagus nerve found in the gut that is responsible for conveying signals to the brain and changes how the brain encodes flavors. A better understanding of how the surgery causes people to avoid fattening food could lead to the development of obesity treatments that mimic the side effect without the need for the surgery itself.[869]

Idiopathic intracranial hypertension (IIH), a condition caused by high pressure within the spaces that surround the brain and spinal cord, is associated with obesity and is most prevalent among women. The most common symptoms are headaches and visual loss, including blind spots, poor peripheral (side) vision, double vision, and temporary episodes of blindness. Although acetazolamide has commonly been used to treat IIH, there was no evidence-based trial supporting its use. The IIH Treatment Trial established that acetazolamide with a low-sodium weight-reduction diet results in modest improvement in visual field function compared with diet alone.[870]

Pulmonary Diseases

There are many different types of pulmonary diseases that affect the lungs and respiratory system. Chronic obstructive pulmonary disease (COPD), for example, has been diagnosed in more than 6 percent of Americans.[871] Another common pulmonary disorder is sleep apnea, in which a person has one or more pauses in breathing or shallow breaths while sleeping. Between 12 and 18 million Americans suffer from sleep apnea,[872] which can increase a person's risk for heart failure, stroke, obesity, diabetes, and high blood pressure.[873] NIH's research on pulmonary diseases seeks to disentangle the complex biological underpinnings of these and other conditions, understand who gets them and why, and to treat and prevent their occurrence.

Understanding Prevalence, Risk Factors, and Underlying Biology

NIEHS-funded researchers found that occupational exposures corresponded to increased morbidity among patients with COPD, accounting for smoking history, demographic factors, and health care utilization. Among those with COPD, occupational exposure was associated with greater disease burden,

[869] Ballsmider LA, et al. *Neural Plast* 2015;2015:601985. PMID: 25722893.
[870] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4362615/.
[871] https://www.cdc.gov/copd/index.html.
[872] https://www.nhlbi.nih.gov/news/spotlight/fact-sheet/sleep-disorders-insufficient-sleep-improving-health-through-research.
[873] https://www.nhlbi.nih.gov/health/health-topics/topics/sleepapnea.

including shorter walk distance, greater breathlessness, reduced quality of life, and increased exacerbation risk.[874]

The NHLBI-funded COPDGene observational study published results showing that, contrary to previous findings, a significant fraction of smokers present radiological and symptomatic signs of lung diseases despite normal respiratory function tests. These results highlight how emerging technologies can shed light on the early phases of tobacco-related lung disease and the shortcomings of currently used diagnostic tests.[875]

Another set of NIEHS-funded scientists found that cigarette smoke induces distinct changes in lung cells, which may be considered as usable biomarkers for cigarette smoke-induced chronic lung diseases. These identified histone marks (histone H3 and histone H4) may play an important role in the epigenetic state during the development of smoking-induced chronic lung diseases, such as COPD and lung cancer. Having biomarkers can allow doctors to identify these diseases earlier and treat them more effectively.[876]

NHLBI launched the Pulmonary Vascular Disease Phenomics (PVDOMICS) Program in 2014. Under this program, teams of investigators will perform comprehensive, deep phenotyping to identify subtypes of pulmonary hypertension and biomarkers of disease that may be useful for early diagnosis or prevention and treatment.[877]

In other research, a 13-year study funded by NHLBI discovered sex-specific differences in cardiovascular risks associated with untreated sleep apnea. Apnea increased the risk of incident heart failure or death in middle-aged women but not men. The risk increased with apnea severity and was stronger in middle-aged women than in elderly women. The findings highlight the importance of evaluating women for sleep apnea and ensuring that women are adequately represented in future clinical studies of sleep apnea.[878]

In a five-year, multi-community study of 5,888 middle-age adults, the risk of developing type 2 diabetes increased 80 percent when apnea was observed during sleep, and 50 percent when symptoms of excessive daytime sleepiness were reported. The risk of diabetes was independent of socio-demographics, lifestyle factors, and medical history. Symptoms of sleep-disordered breathing are easily reported and may identify individuals at high risk for diabetes who might benefit from medical management.[879]

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[874] Ahmad T, et al. *FASEB J* 2015;29(7):2912-29. PMID: 25792665.
[875] Regan EA, et al. *JAMA Intern Med* 2015;175(9):1539-49. PMID: 26098755.
[876] Sundar IK, et al. *J Proteome Res* 2014;13(2):982-96. PMID: 24283195.
[877] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-030.html.
[878] Roca GQ, et al. *Circulation* 2015;132(14):1329-37. PMID: 26316620.
[879] Strand LB, et al. *Diabetes Care* 2015;38(11):2050-8. PMID: 26384390.

Improving Treatment and Prevention

In 2014, NHLBI made awards for the Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases II (CADET II) program to stimulate development of new drugs and diagnostics for lung diseases and sleep-disordered breathing. Groups funded under the program are developing new drugs to treat asthma, COPD, pulmonary hypertension, sleep-disordered breathing, and idiopathic pulmonary fibrosis.[880,881,882,883]

In 2015, NHLBI awarded grants under the Pulmonary Trials Cooperative (PTC). This new mechanism allows for multiple trials to be conducted simultaneously and served by single Network Management Core, so as to accelerate the pace of clinical discovery in COPD. Three COPD trials are underway, targeting different types of COPD patients, ranging from those with early disease to those with very severe COPD.[884]

Some prior studies have shown that statins were beneficial in patients with COPD. However, an NHLBI-funded clinical trial found that COPD patients without cardiovascular disease who were treated with simvastatin did not receive any benefit from the treatment.[885]

NHLBI-funded research has demonstrated that pulmonary macrophage transplantation was effective in treating a mouse model of hereditary pulmonary alveolar proteinosis, a rare childhood lung disease. Further refinement of this approach could lead to a therapy for people with this condition.[886]

NIEHS-supported researchers measured particulate matter (PM) exposure with aerodynamic size less than or equal to 2.5 (PM2.5) among 84 patients with COPD, 56 percent of whom were obese (with a body mass index greater than or equal to 30 kg/m^2), all former smokers with moderate-to-severe COPD. The study results indicate that obesity modified the effects of indoor PM on COPD respiratory outcomes, where obese patients exhibited exaggerated exacerbations related to PM exposure such as wheeze and airway and systemic inflammatory responses.[887]

Another set of NIEHS grantees are epigenetically activating the human CC16 gene in lung cells. The researchers hypothesize this gene will be protective in lung responses to smoke-induced injury in COPD. An aim of this project is to help determine potential therapeutic value of this approach in cells from

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[880] http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-supports-cadet-researchers-produce-new-pulmonary-disease-drugs.
[881] http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-supports-cadet-researchers-produce-new-pulmonary-disease-drugs-part-2.
[882] http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-supports-cadet-researchers-produce-new-pulmonary-disease-drugs-part-3.
[883] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-001.html.
[884] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-015.html.
[885] Criner GJ, et al. *N Engl J Med* 2014;370(23):2201-10. PMID: 24836125.
[886] Suzuki T, et al. *Nature* 2014;514(7523):450-4. PMID: 25274301.
[887] McCormack MC, et al. *Eur Respir J* 2015;45(5):1248-57. PMID: 25573407.

COPD patients. If the aims are achieved, this study will support subsequent testing of a novel approach in pre-clinical models of COPD followed by randomized clinical trials in COPD patients.[888]

In 2014, NHLBI initiated the Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network to support at least three randomized controlled clinical trials focused on preventing or treating patients who have, or are at risk for, acute lung injury or acute respiratory distress syndrome.[889,890]

Substance Use and Addiction

Nearly four decades of research supported by NIH have proven substance addiction to be a complex brain disease characterized by compulsive—at times uncontrollable—drug or alcohol craving, seeking, and use that persists despite potentially devastating consequences. In 2015, more than 33,000 people in the U.S. died of opioid overdose;[891] approximately 88,000 die an alcohol-related death each year.[892] Substance use and addiction affects Americans from every race, ethnicity, sex, gender, age group, and socioeconomic class. Understanding, preventing, and treating disorders, such as opioid use disorder and fetal alcohol spectrum disorder, require a comprehensive research portfolio that explores the complex biological, clinical, social, and epidemiological factors that contribute to substance use and addiction. NIH, led by NIAAA and NIDA, invests in all areas of substance use and addiction research toward that goal of understanding, preventing, and treating conditions that cause millions of Americans and their families to suffer.

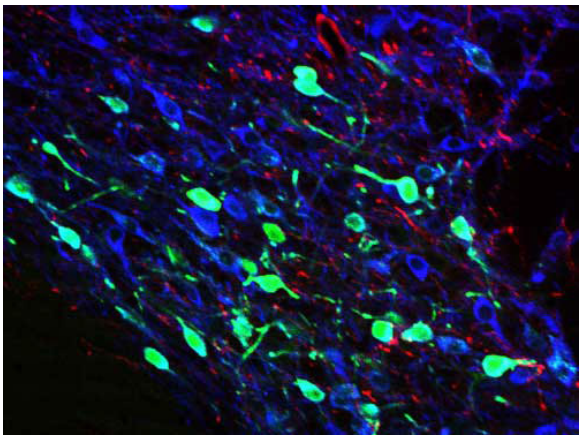

Figure 36. Partial view of labelled neurons in the reward circuitry of the brain. Credit: NIDA.

Understanding Prevalence, Risk Factors, and Underlying Biology

A recent study based on data collected through NIAAA's National Epidemiological Survey on Alcohol and Related Conditions (NESARC III) found that nearly one-third of adults in the U.S. have alcohol use

[888] https://projectreporter.nih.gov/project_info_details.cfm?aid=8872666&icde=34716046.
[889] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-014.html.
[890] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-015.html.
[891] https://www.cdc.gov/mmwr/volumes/65/wr/mm655051e1.htm.
[892] https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics.

disorder (AUD) at some time in their lives, but only about 20 percent of them seek AUD treatment. The researchers found that rates of AUD were greater among men than women, and that among adults ages 18–29, more than 7 percent had AUD within the past year. In a separate study based on NESARC III data, researchers found that about 10 percent of American adults have had drug use disorder at some time in their lives, and that drug use disorder co-occurs with a range of mental health disorders and often goes untreated. The results also revealed that drug use disorder was more common among men, and White and Native American individuals.[893]

According to an NICHD-supported analysis of more than half a million women in a large, commercial insurance plan who delivered babies between 2005 and 2011, more than 14 percent were prescribed opioid pain-relievers at some point during their pregnancy. Most of these prescriptions were for short courses of treatment for less than a week for such conditions as back, abdominal, or joint pain or migraines, although 2.2 percent of the pregnant women received three or more courses of the drugs. Results suggest that the use of opioids during pregnancy—without adequate data on their effects on the developing fetus—may be more common than previously thought.[894]

The misuse of prescription drugs such as opioids is a major public health concern. A contract supported through the SBIR program was awarded in July 2014 for the creation of a Prescription Drug Abuse Policy System (PDAPS), to provide user-searchable access to authoritative, detailed, and comparable information on prescription drug misuse related laws and policies in the U.S. at the state and federal levels. PDAPS will primarily be a tool for researchers to encourage and facilitate analyses on the effects and effectiveness of prescription drug-related policies.

The annual Monitoring the Future (MTF) survey, supported by NIDA, surveys 8th, 10th, and 12th graders to reveal drug use trends and inform prevention and treatment strategies targeted at youth and young adults. Each year, MTF surveys more than 48,000 students to gain an understanding of the prevalence of substance use among adolescents; the perceived availability of drugs, alcohol, and tobacco; and the risk they perceive in using substances. [895]

Human brain imaging studies have shown that over the course of adolescence, the volume of gray matter in the brain decreases, likely reflecting the normal process of synaptic pruning, whereas the volume of white matter increases, presumably reflecting enhanced brain connectivity. The nature of these rapid changes makes the developing adolescent brain particularly vulnerable to the adverse effects of alcohol. In a recent NIAAA-supported study, researchers used neuroimaging to assess the developmental trajectory of 134 adolescents, ages 12–24, over 8 years. Of these youth, 75 transitioned to heavy drinking during a 3.5-year period. The results showed that heavy drinking adolescents had accelerated reductions in gray matter and attenuated increases in white matter, compared to non-

[893] Grant BF, et al. *JAMA Psychiatry* 2015;72(8):757-66. PMID: 26039070.
[894] Bateman BT, et al. *Anesthesiology* 2014;120(5):1216-24. PMID: 24525628.
[895] https://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future.

drinking adolescents. This study provides further evidence that heavy drinking during adolescence alters brain development.[896]

Previous research has shown an association between excessive adolescent alcohol use and deficits in brain structure and function. However, it is not clear whether the deficits predated the onset of alcohol use or occurred as a consequence of it. In FY 2014 and 2015, NIAAA continued to support the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), a multisite longitudinal study to elucidate the effects of alcohol exposure on the developing human brain and identify brain characteristics that may predict AUD and onset or worsening of mental illness during adolescence and/or adulthood. The five NCANDA sites have enrolled more than 800 youth, ages 12–21, and will capture brain images as well as psychological and behavioral data from these participants before and after they start to drink. NCANDA has laid the foundation for the larger and more extensive ABCD study (see below) supported under the CRAN initiative.[897]

In September 2015, NIDA, NIAAA, NCI, and other NIH Institutes and Offices launched the Adolescent Brain Cognitive Development (ABCD) Study. The study is recruiting approximately 10,000 children ages 9–10, most of whom will not have initiated substance use, and following them into early adulthood. Participants' exposure to alcohol and other drugs (alone and in combination), academic achievement, cognitive skills, mental health, and brain structure and function will be tracked over a ten-year period. The findings 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. It is hoped that the findings will inform prevention and treatment interventions and public health strategies.[898]

To better understand how risks of substance use may change over time in young people, NICHD-supported researchers analyzed data from the National Longitudinal Study of Adolescent Health. They found that gender differences in smoking and regular binge drinking changed with age. For example, around age 16, girls were more likely than boys to be smokers, but by age 17.5, more boys than girls were smokers, and the gender gap persisted for the rest of adolescence and adulthood. Racial and ethnic disparities also varied over time for smoking, regular binge drinking, and marijuana use. All three behaviors were most prevalent among White teens, but the prevalence of smoking and binge drinking among Hispanic and Black individuals continued to rise through their 20s. Understanding these differences in substance use patterns may help in developing targeted interventions to assist teens and young adults when they are most at risk.[899]

NIAAA is investing in research to define the underlying neurobiological mechanisms through which repeated exposure to alcohol during adolescence causes long-lasting structural and functional abnormalities in the brain. A study conducted by NIAAA's Neurobiology of Adolescent Drinking in Adulthood Consortium found that animals exposed to alcohol during adolescence exhibited epigenetic

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[896] Squeglia LM, et al. *Am J Psychiatry* 2015;172(6):531-42. PMID: 25982660.
[897] http://www.ncanda.org.
[898] http://www.niaaa.nih.gov/news-events/news-releases/nih-launches-landmark-study-substance-use-and-adolescent-brain-development.
[899] Evans-Polce RJ, et al. *Addict Behav* 2015;41:218-22. PMID: 25452068.

changes (i.e., changes affecting gene expression that do not alter the DNA sequence) in the amygdala, a brain region in humans that regulates emotional responses and the brain's stress system. These changes were associated with increased alcohol consumption and anxiety-like behaviors in adulthood. Specifically, expression of genes involved in forming connections between nerve cells in the amygdala decreased; reversal of these epigenetic effects resulted in reduced alcohol intake and less anxiety in the adult animals.[900]

Previous studies have demonstrated that heavy binge drinking is associated with reduced white matter integrity in various brain structures in both adolescents and alcohol-dependent adults. In a recent study, researchers used rodent models of adolescent binge drinking and adult alcohol dependence to gain insight into how alcohol affects white matter integrity in the frontal cortex of the brain, the region responsible for executive function in humans. They found that adolescent binge drinking was associated with damaged myelin (the substance which comprises white matter) in the medial prefrontal cortex in adulthood, reduced density of myelin in the medial prefrontal cortex in adolescence, and worse performance on a working memory task in adulthood. These results suggest that adolescent binge drinking may affect white matter integrity in the medial prefrontal cortex through reduction of myelin, and that these changes may contribute to deficits in executive function in adulthood.[901]

Binge drinking increases risk for acute negative consequences, such as violence and injuries, and longer term consequences, such as alcohol use disorder and anxiety disorders. Previous studies have shown that binge alcohol use in mice elevates activity of corticotropin-releasing factor (CRF, a stress neuropeptide) that increases alcohol drinking and anxiety-like behavior, while neuropeptide Y (NPY, an anti-stress neuropeptide) reduces both binge alcohol use and anxiety-like behavior. NIAAA-supported researchers investigated a region of the brain called the bed nucleus of the stria terminalis (BNST) to gain insight into the underlying interactions between CRF and NPY in the regulation of binge alcohol consumption. They found that in the mouse BNST, activation of NPY receptors suppressed binge alcohol consumption by enhancing inhibition of CRF neurons, demonstrating that the BNST is a site at which stress and anti-stress systems interact to modulate binge alcohol consumption, and paving the way for new treatment targets for alcohol use disorder.[902]

In FY 2015, ORWH funded an administrative supplement seeking to identify gender differences in inhibitory control and treatment of inhibitory control.[903] Problems with inhibitory control is hypothesized to lead to a range of problems including excessive alcohol use, tobacco use, and unhealthy eating. The research findings have the potential to be scaled up into a flexible, low-cost, and wide-ranging intervention to remediate some of the effects of early adversity on inhibitory control and thus a number of prevalent health risking behaviors.

Approximately one-third of individuals who have had PTSD have AUD at some point in their lives, and an estimated 30–60 percent of patients seeking treatment for AUD meet criteria for PTSD. Research

[900] Pandey SC, et al. *Neurobiol Dis* 2015;82:607-19. PMID: 25814047.
[901] Vargas WM, et al. *J Neurosci* 2014;34(44):14777-82. PMID: 25355229.
[902] Pleil KE, et al. *Nat Neurosci* 2015;18(4):545-52. PMID: 25751534.
[903] https://projectreporter.nih.gov/project_info_description.cfm?aid=8994031&icde=34700137.

suggests that alcohol use may increase risk for PTSD by altering the brain's ability to recover from traumatic experiences. In a study conducted by the NIAAA IRP, scientists investigated the role of a key synaptic plasticity molecule, postsynaptic density 95 (PSD-95), in the stability and persistence of fear memories. Genetically interfering with a PSD-95 in the prefrontal cortex of the brain in mice led to a significant weakening of fear memories. Targeting PSD-95-related mechanisms represents a novel approach to alleviating trauma-related anxiety disorders associated with AUD.[904]

Heavy methamphetamine users frequently have substantial problems with their teeth and gums. The term *meth mouth* has been anecdotally used to describe the rampant oral disease typically found in this population. NIDCR-funded researchers looked at a large community sample of methamphetamine users, documenting significant levels of caries (cavities) and periodontal disease. This study was one of the first to provide this level of detail on the extent of damage in the oral cavity due to methamphetamine use, leading the way for future research and treatments for this population.[905]

Figure 37. Researchers at NIDA are working to identify new medications for treating drug addiction. Credit: NIH.

Located in ODP within the NIH OD, the Tobacco Regulatory Science Program (TRSP) continued to support new and ongoing research in FY 2014 and 2015 for the NIH-FDA interagency partnership on tobacco regulatory science. To fill gaps in the existing research portfolio, TRSP funded 72 new grants, bringing total FY 2014 and 2015 extramural spending on tobacco regulatory science to $214 million. The new grants focus on research in tobacco flavors and flavorings, public displays of harmful and potentially harmful constituents' information, and other research that could help inform FDA regulatory authority over the marketing, manufacturing, and distribution of tobacco products.

Improving Treatment and Prevention

To reduce the gap between publication of research results and impacts on treatment delivery, NIDA developed the Blending Initiative, in collaboration with the Substance Abuse and Mental Health Services

[904] Fitzgerald PJ, et al. *Mol Psychiatry* 2015;20(7):901-12. PMID: 25510511.
[905] Dye BA, et al. *BMC Oral Health* 2015;15:76. PMID: 26143495.

Administration (SAMHSA).[906] This initiative supports the development of user-friendly treatment tools and educational products to facilitate adoption of research-based interventions into front-line clinical settings. Through this initiative, NIDA and SAMHSA's Addiction Technology Transfer Centers (ATTCs) disseminate treatment and training products based on NIDA-supported research. The ATTC network consists of 10 regional centers, four national focus area centers, and a network coordinating office that serves all 50 U.S. states, Washington, D.C., and U.S. territories. Conferences that will foster collaboration and knowledge exchange between drug use researchers and treatment providers are a keystone of the initiative; the first, a workshop on prescription opioid misuse, was held in 2014.[907]

In 2015, the Secretary of HHS launched an initiative to address the complex problem of prescription opioid and heroin addiction and overdose in this country that emphasizes the implementation of evidence-based prevention and treatment strategies to improve prescribing practices, deployment of the medication naloxone to reverse overdoses, and access to medication-assisted treatment (MAT) to treat opioid use disorders. NIDA is an active partner in these efforts and is focused on supporting research and disseminating findings to improve opioid-prescribing practices, expand the use of naloxone, improve the integration of MAT pharmacotherapies such as buprenorphine, methadone, and naltrexone into treatment services in primary and specialty care, and to develop more effective pain treatments with reduced potential for misuse and diversion.

NIDA has been at the forefront of helping to develop new pharmaceutical treatments for opioid addiction and overdose. For example, FDA approved Narcan nasal spray on November 18, 2015. Narcan is an easy-to use, needle-free alternative to injectable naloxone for use during a suspected opioid overdose. The product is a result of a partnership between NIDA and Lightlake Therapeutics Inc., marketed by Adapt Pharma Limited, a partner of Lightlake Therapeutics.[908]

NIDA's Clinical Trials Network launched the first large-scale study on treatment of prescription opioid addiction in 2007 at ten treatment sites around the country. Outpatients addicted to prescription opioids received Suboxone (buprenorphine plus naloxone) in combination with counseling sessions or brief standard medical management. Approximately 49 percent of patients reduced their prescription pain reliever misuse while on Suboxone; however, this success rate dropped to 8.6 percent once the Suboxone was discontinued, suggesting the need for longer medication maintenance and more research to determine the required duration. The investigators continued to follow participants for several years after the completion of the trial. Overall, participants showed substantial improvement from baseline to the 18-month follow-up, at which point only 16.3 percent were opioid dependent. Analyses of data collected at the 30-month and 42-month follow-up assessments began in 2015.[909]

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[906] https://www.drugabuse.gov/nidasamhsa-blending-initiative.
[907] https://www.drugabuse.gov/blending-initiative/blending-meetings/empowering-family-medicine-residencies-to-address-prescription-opioid-abuse.
[908] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM473505.
[909] http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies/prescription-opioid-addiction-treatment-study-poats.

It is imperative to identify and effectively treat individuals with opioid use disorders, but evidence-based MAT strategies are often not used or are restricted in ways that decrease their efficacy. A study exploring outcomes associated with tapering patients off of buprenorphine, a partial opioid agonist, over a nine-week period of time (after six weeks of stabilization), demonstrated that maintenance buprenorphine therapy is more effective than tapering and discontinuation of the medication in treating prescription opioid-dependent patients in primary care settings.[910]

The *NIDAMED* website[911] provides evidence-based resources to help medical students, residents, practicing physicians, and other healthcare clinicians identify patient drug use early to prevent it from escalating to addiction, as well as to identify and refer patients in need of specialized addiction treatment. Several training tools have been generated. For example, from 2007 to 2014, NIDA partnered with the American Medical Association's to establish the NIDA Centers of Excellence (COEs) for Physician Information to create 12 curriculum resources about substance use, addiction, and health consequences, six focusing specifically on prescription pain medication misuse. These resources are available on the *NIDAMED* website and through the individual COEs. The *NIDAMED* initiative, with funding from ONDCP and in partnership with Medscape, created two continuing education modules on safe prescribing of opioids for pain and managing patients who misuse prescription opioids. From 2012 to 2016, 115,323 clinicians completed the modules and clinicians continue to access the unaccredited versions on the *NIDAMED* website. NIDA also established a Coalition of Healthcare Organizations to work collaboratively to develop a CME/CE on clinical strategies to prevent and address adolescent substance use and prescription medication misuse. This continuing education module will be launched in summer 2016 and is targeted to clinicians across the professional spectrum.

NIDA's Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS) program was launched in 2013. It is a seven-site cooperative research program featuring three studies designed to identify and test strategies for improving the delivery of evidence-based substance use and HIV prevention and treatment services for justice-involved youth. A nationally representative survey of the juvenile justice system was conducted to ascertain policies and practices related to substance use assessment and service delivery in juvenile justice settings across the U.S. These data are being analyzed, and findings are expected in FY 2016. In addition, an organizational level intervention is currently being tested in 36 juvenile justice systems across the country and includes training on evidence-based practices to target youth substance use, data driven decision making, and goal setting.

From 2002 to 2014, NIDA funded the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) program, a multisite research cooperative focused on rapidly moving promising science-based addiction treatments into community settings, to improve existing drug treatment for criminal justice populations, and to inform the development of integrated treatment models. The CJ-DATS program included testing of Medication-Assisted Treatment Implementation in Community Correctional Environments (MATICCE) and HIV Services and Treatment Implementation in Corrections (HIV-STIC). Through these studies, CJ-DATS contributed to a significant body of research—14 peer-reviewed publications—describing existing

[910] Fiellin DA, et al. *JAMA Intern Med* 2014;174(12):1947-54. PMID: 25330017.
[911] https://www.drugabuse.gov/nidamed-medical-health-professionals.

treatment practices in the criminal justice system, developing and testing the effectiveness of specific interventions, and exploring strategies for implementation and quality improvement of addiction treatment programs for criminal justice populations.

NIDA developed *Family Checkup*, an online resource that equips parents with research-based skills to help keep their children drug-free. NIDA-funded research has shown the critical role parents play in preventing their children from using drugs. *Family Checkup* poses questions for parents to consider as they interact with their children, highlighting parenting skills that are important in preventing the initiation and progression of drug use among youth. The tools were developed by the Child and Family Center at the University of Oregon.[912]

Communities that Care, a program developed with NIDA support, is a process for community coalitions to identify risk and protective factors for substance use at the community level, and to select and implement evidence-based prevention interventions to decrease risk and increase protective factors for youth. A panel of more than 4,000 youth was recruited, beginning in 5th grade and followed through 12th grade. A benefit–cost analysis study of the program's operating system on delinquency and substance use outcomes at 12th grade found that Communities that Care was cost beneficial, with a benefit–cost ratio of $8.22 per dollar invested.

Another prevention program supported by NIDA is the Universal Prevention Interventions program. In three randomized controlled trials, researchers tested the long-term effects of three universal preventive intervention programs delivered to middle school students residing in small towns and rural communities: the Iowa Strengthening Families Program (ISFP), a family-focused intervention; the Strengthening Families Program: For Parents and Youth 10–14 plus the school-based Life Skills Training (SPF 10–14 + LST); and the SFP 10–14 plus one of three school-based interventions with implementation guided by the Promoting School-Community-University Partnerships to Enhance Resilience (PROSPER) partnership delivery system. At ages 17–25, 6 to 14 years after initial program implementation, students who received any of these three prevention programs were less likely to develop addiction. The interventions were found to be comparable or even more effective for higher risk subgroups, who had initiated substance use early.

NIDA has partnered with the Center for Substance Abuse Research (CESAR) to create a coordinating center for the National Drug Early Warning System (NDEWS). NDEWS was launched in August 2014 and serves as the first national public health surveillance system with the ability to identify emerging drug threats (i.e., new synthetic drugs). NDEWS generates critically needed information about local drug use trends and their public health consequences so that rapid, informed, and effective public health responses can be developed at the national, state, and local levels. The NDEWS network includes scientists, public health experts, law enforcement representatives, and others who are part of a virtual community sharing information and assisting with local research. It utilizes both traditional and innovative sources, including social media, Web scans, and information from poison control centers, and harmonizes community indicators for tracking drug trends nationally and in 12 sentinel sites. NDEWS

[912] http://www.drugabuse.gov/family-checkup.

has also established a Rapid Response Team (RRT) to conduct local studies of emerging drugs. NDEWS Alerts and annual reports are used to disseminate findings to a large virtual community and on the NDEWS website.

Researchers supported by the Common Fund's Science of Behavior Change program have shown that smoking cessation programs offering financial incentives are more effective than standard approaches, such as free counseling or nicotine replacement therapy.[913] Interestingly, providing a monetary reward for quitting smoking was less effective than a combination of providing a smaller reward plus requiring participants to make a deposit that would be lost if they failed to quit. These results suggest that financial incentive programs may be an effective approach to promoting healthy behavior.[914,915,916]

As cigarette smoking decreased in the U.S., water pipe tobacco smoking increased. Water pipe tobacco consumption is particularly prevalent among adolescent and young adult populations. One NCI- and OBSSR-funded study used a two-phase approach to create recommendations for controlling water pipe tobacco use. This award resulted in a longitudinal study in the U.S., showing increased use of cigarettes later in life among young adults and adolescents who used water pipes for tobacco or smokeless tobacco products.[917,918]

The extent of binge drinking and related consequences such as blackouts, physical and sexual assaults, alcohol poisonings, injuries, and deaths on college campuses is alarming. In September 2015, NIAAA released the College Alcohol Intervention Matrix (CollegeAIM), an evidence-based decision tool to help college and university administrators select interventions for addressing harmful and underage drinking on their campuses. CollegeAIM compares and rates nearly 60 individual and environmental interventions on effectiveness, anticipated costs, barriers to implementation, and other factors. Developed by leading college alcohol researchers and NIAAA staff, this comprehensive tool uses a simple matrix that informs college staff about alcohol strategies and guides them to evidence-based interventions.[919]

Despite the availability of effective behavioral and pharmacological treatments for AUD, fewer than one in five individuals with AUD receive treatment. NIAAA is working to increase public awareness of evidence-based treatment for AUD and released *Treatment for Alcohol Problems: Finding and Getting Help*, which outlines behavioral and medication treatment options for AUD and provides tips for selecting among treatment options and sustaining recovery.[920]

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[913] https://commonfund.nih.gov/behaviorchange
[914] Halpern et al. *N Engl J Med* 2015;372(22):2108-17.PMID: 25970009.
[915] http://www.nytimes.com/2015/05/14/health/study-asks-if-carrot-or-stick-can-better-help-smokers-stop.html.
[916] http://www.npr.org/sections/health-shots/2015/05/13/406459255/smokers-more-likely-to-quit-if-their-own-cash-is-on-the-line.
[917] Soneji S, et al. *JAMA Pediatr* 2015;169(2):129-36. PMID: 25485959.
[918] https://projectreporter.nih.gov/project_info_description.cfm?aid=8929177&icde=34714631.
[919] http://www.collegedrinkingprevention.gov/collegeaim/.
[920] http://pubs.niaaa.nih.gov/publications/treatment/treatment.htm.

Current medications approved for treating AUD are nonaddictive and work well in combination with behavioral therapies; however, fewer than 4 percent of individuals with AUD are prescribed a medication. To better inform clinicians and to raise public awareness, NIAAA partnered with SAMHSA to develop *Medication for the Treatment of Alcohol Use Disorder: A Brief Guide* for health care providers on the use of medications in the treatment of AUD.[921]

In 2015, NIAAA issued the *Wearable Alcohol Biosensor Challenge* to stimulate the design of a discreet, noninvasive wearable device capable of measuring blood alcohol levels in near real-time. An improved alcohol biosensor could be a valuable resource for the alcohol research community, decreasing reliance on participant self-reporting in scientific studies. The winning prototype of the challenge was BACtrack Skyn, a device that is worn on the wrist and offers continuous and noninvasive monitoring of a user's blood alcohol level. It uses fuel cell technology similar to devices used by law enforcement in roadside alcohol testing. BACtrack, a company known nationally for designing and selling portable breath alcohol testers for consumer and professional use, was the recipient of the $200,000 first prize.[922]

Three medications—acamprosate, disulfiram, and naltrexone—have been approved by FDA for the treatment of alcohol use disorder; however, they are not widely prescribed. To evaluate the benefits and harms of medications for the treatment of adults with AUD, researchers conducted a systematic review and meta-analysis of AUD treatment studies. They found that acamprosate and oral naltrexone have the best evidence supporting their benefits and were equally effective at preventing a return to drinking any amount of alcohol. Oral naltrexone was also associated with a reduction in a return to heavy drinking, and injectable naltrexone was found to reduce the number of heavy drinking days.[923]

The NIAAA Clinical Investigations Group (NCIG) is a key NIAAA medications development program established to streamline and expedite the process for developing AUD medications by conducting fast-success/fast-fail Phase II clinical trials with a turnaround time of 18 months. In June 2015, NCIG initiated a study to test the safety and efficacy of an extended-release formulation of gabapentin enacarbil, an FDA-approved medication for restless leg syndrome and shingles-related nerve pain. This study, which is being conducted in collaboration with the biopharmaceutical company XenoPort, is expected to be completed in 2016.[924]

To encourage alcohol screening for youth, NIAAA continued to promote and disseminate *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide* to assist health care providers in identifying alcohol use and AUD in youth ages 9–18, and to identify risk for alcohol use, especially for younger children. The guide provides 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 is supporting six studies to evaluate the effectiveness of the guide as a predictor of

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[921] http://store.samhsa.gov/shin/content//SMA15-4907/SMA15-4907.pdf.
[922] http://www.niaaa.nih.gov/news-events/news-releases/niaaa-selects-winners-its-wearable-alcohol-biosensor-challenge.
[923] Jonas DE, et al. *JAMA* 2014;311(18):1889-900. PMID: 24825644.
[924] http://www.niaaa.nih.gov/news-events/news-releases/nih-begins-clinical-trial-new-medication-alcohol-use-disorder.

alcohol risk, alcohol use and AUD, and as an initial screen for other behavioral health problems in healthcare, academic, and juvenile justice settings. A recent study conducted with youth ages 12–20 at primary care clinics in rural Pennsylvania found that the NIAAA youth guide's alcohol risk guidelines for moderate risk and highest risk were effective screens for AUD.[925,926,927]

Transplantation

Since the first successful kidney transplant between identical twins in 1954, transplantation has become the treatment of choice for end-stage organ failure. Despite tremendous progress, however, major barriers still remain to the overall success of transplantation. These 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 anti-rejection therapies.

Organ transplantation is standard therapy for end-stage liver or kidney disease, prolonging survival and improving quality of life. However, at the turn of the 21st century, organ transplantation was unavailable to those infected with HIV due to concerns about disease transmission, the fear that pharmacologic immunosuppression to prevent rejection would hasten progression from HIV to AIDS, and the lingering stigma associated with HIV infection. NIAID supported the Solid Organ Transplantation in HIV Multi-Site Study, which provided the clinical outcomes that led to the HIV Organ Policy Equity (HOPE) Act, which was signed on November 11, 2013. This act removed the statutory ban on recovering HIV-positive (HIV+) organs and allows for transplantation of HIV+ organs into HIV+ recipients. NIAID assisted with the implementation and development of safety guidelines and protocols, which were published in the *Federal Register* on November 25, 2015.[928]

Acute graft-versus-host disease (GVHD), a medical complication occurring when transplanted cells recognize the recipient's tissue as foreign and attack it, is a significant risk in unrelated donors. NIAID-funded researchers identified a genetic component associated with higher risk of GVHD. Genotyping of bone marrow transplant recipients showed that the high expression allele of human leukocyte antigen HLA-DPB1 is associated with a higher risk of GVHD.[929]

NIAID intramural investigators reported the first successful haploidentical (imperfectly matched) transplantation using post-transplant high-dose cyclophosphamide (PTCy) in a 12-year-old boy with chronic granulomatous disease (CGD) and an ongoing fungal infection. The success of this procedure in

[925] http://www.niaaa.nih.gov/publications/clinical-guides-and-manuals/alcohol-screening-and-brief-intervention-youth.
[926] Clark DB, et al. *J Pediatr* 2016;173:214-20. PMID: 27059911.
[927] http://www.niaaa.nih.gov/news-events/news-releases/study-supports-single-question-alcohol-screen-adolescents.
[928] https://www.federalregister.gov/articles/2015/11/25/2015-30172/final-human-immunodeficiency-virus-hiv-organ-policy-equity-hope-act-safeguards-and-research-criteria.
[929] Petersdorf EW, et al. *N Engl J Med* 2015;373(7):599-609. PMID: 26267621.

this most challenging case provides sufficient grounds for exploring this as an acceptable transplant procedure for patients with no suitable matched sibling or unrelated donor.[930]

NIAID and NCI investigators successfully performed matched and unmatched hematopoietic cell transplantation in six patients with mutations in the dedicator-of-cytokinesis-8 (DOCK8) gene. The DOCK8 deficiency results in a constellation of clinical symptoms that encompass allergic/atopic manifestations, infection, and malignancy. All patients achieved rapid and high levels of donor engraftment and complete reversal of the clinical and immunologic phenotype with a low incidence of regimen-related toxicity.[931]

In a 2014 breakthrough in treating SCD, NHLBI and NIDDK intramural investigators successfully reversed SCD in nearly all of the patients who received a partial-ablation bone marrow transplant. In this method, roughly half of the bone marrow, instead of all of it, is replaced with healthy donor stem cells from immunologically matched family donors. In addition, half of the patients were able to stop taking immunosuppressant drugs one year after the transplant. Plus, after years of careful monitoring, none of these patients have experienced transplant rejection or graft-versus-host disease. NHLBI intramural investigators are now working to extend this treatment to patients who do not have a perfectly matched donor.[932,933]

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 healthcare expenditures, and may lead to substantial disability and impaired quality of life. For example, based upon national public health surveys conducted over several years, it is estimated that 1 in 10 U.S. adults 18 years of age and older suffer from daily urinary incontinence, and most of those affected are women.[934] Gynecologic conditions such as uterine fibroids, endometriosis, adenomyosis, ovarian cysts, and menstrual disorders account for a significant amount of suffering for 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.[935] Spearheaded by NIDDK and NICHD, 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.

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[930] Parta M, et al. *J Clin Immunol* 2015;35(7):675-80. PMID: 26453586.
[931] Cuellar-Rodriguez J, et al. *Biol Blood Marrow Transplant* 2015;21(6):1037-45. PMID: 25636378.
[932] Hsieh MM, et al. *JAMA* 2014;312(1):48-56. PMID: 25058217.
[933] http://www.nhlbi.nih.gov/news/press-releases/2014/adults-stop-anti-rejection-drugs-after-partial-stem-cell-transplant-0.
[934] https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/Pages/urologic-diseases-america.aspx..
[935] https://www.nichd.nih.gov/about/org/der/branches/ghdb/programs/Pages/gynecologic-diseases-disorders.aspx.

Understanding Prevalence, Risk Factors, and Underlying Biology

Scientists at NIH have solved a long-standing mystery about the origin of one of the cell types that make up the ovary. The team also discovered how ovarian cells share information during development of an ovarian follicle, which holds the maturing egg. Researchers believe this new information on basic ovarian biology will help them better understand the cause of ovarian disorders, such as premature ovarian failure and polycystic ovarian syndrome; both conditions that result in hormone imbalances and infertility in women.[936]

Fibroids are benign tumors that develop in the uterus and are the most common noncancerous tumors in women of childbearing age. They can cause painful symptoms and abnormal bleeding from the uterus, and can also make it difficult for a woman to get pregnant or maintain a pregnancy. In an NICHD study of possible relationships between environmental chemicals and the development of fibroids, researchers are collecting blood and urine samples, along with other specimens, from women with fibroids and are testing them for different environmental chemicals.[937]

Infertility may result from many causes, including urologic or gynecologic disorders, or modifiable lifestyle factors. In another NICHD study, researchers seek to better understand the causes of infertility. Researchers in he Impact of Diet, Exercise, and Lifestyle on Fertility (IDEAL) study are collecting data on lifestyle factors, along with biospecimens, for couples who are having trouble starting a family. In addition to the pre-pregnancy data, researchers will also collect data on pregnancy outcomes for women who conceive during their enrollment in the study. [938]

Understanding the factors governing development and function of the genitourinary tract could facilitate approaches to replace or repair damaged tissues. The NIDDK-led GenitoUrinary Development Molecular Anatomy Project (GUDMAP) project is cataloging cell types in mice for each organ, the genes that mark these cells and those that are required for their function, the regulatory factors that induce or maintain the various cell types, and the developmental and anatomic relationships of each cell type to its neighbor in the GU tract. GUDMAP has been enhanced by a project to map pain receptors in the urinary tract and pelvic region, which will contribute to knowledge of overall neuroanatomy. These efforts could contribute to understanding and addressing certain reproductive health problems, such as those resulting from congenital malformations in external genitalia in both males and females, and neurogenic bladder from spina bifida and other causes.[939,940]

The term lower urinary tract symptoms, or LUT symptoms, is used to refer to symptoms associated with any type of lower urinary tract dysfunction or condition (e.g., urinary incontinence (UI), urinary tract infections (UTIs), benign prostatic hyperplasia (BPH)), as well as those with as-yet unidentified cause. LUT symptoms—which can include frequent or urgent urination, needing to get up multiple times at

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[936] https://www.nih.gov/news-events/news-releases/nih-study-solves-ovarian-cell-mystery-shedding-new-light-reproductive-disorders.
[937] https://www.nichd.nih.gov/about/org/diphr/Documents/DIPHR_2015_Annual_Report.pdf.
[938] https://www.nichd.nih.gov/about/org/diphr/eb/research/Pages/IDEAL.aspx.
[939] http://www.gudmap.org/About/index.html.
[940] https://www.gudmap.org/About/Projects/ngudmap.html.

night to urinate, and problems with voiding—and their associated conditions not only have a direct negative impact on health, but also exacerbate or contribute to other challenges, including social, mental, and physical health problems. To better address the burden of lower urinary tract dysfunction (LUTD), researchers need to learn more about the nature of LUT symptoms (LUTS), how they affect patients, and their fundamental causes. The NIDDK-sponsored Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) is recruiting participants in a multi-faceted effort to (1) improve the measurement of individual experiences of LUTS by developing new patient questionnaires; (2) better define the phenotypes of men and women with LUTS; and (3) identify potential biomarkers or other tools that could be useful in developing future prevention or intervention strategies. Through these activities, investigators hope to inform strategies to prevent or manage disease and improve the lives of people who suffer from LUTS.[941]

Urgency urinary incontinence (UUI), sometimes called overactive bladder, affects thousands of women in the U.S., and the cause is often unclear. Although prescription drugs and/or behavioral treatments help many women, others have persistent symptoms. NICHD-supported researchers explored whether bacteria in the bladder might be related to UUI, even in women without any signs of a bladder or urinary tract infection. In about 180 women with UUI, about half had unexpected bacteria in their urine, although they had no symptoms or other signs of infection. Women with urinary bacteria had a higher number of daily UUI episodes before treatment, responded better to treatment, and were less likely to develop urinary tract infection. The results suggest that previously undetected bacteria in the bladder may have a role in UUI in women.[942]

The neutrophil and other cells lining the bladder produce the pro-inflammatory molecule COX-2 during infection. While COX-2 is not detectable in the uninfected bladder, it is found in women with UTIs. Blocking COX-2 activity with an inhibitor reduced the severity of bladder inflammation and protected mice from chronic UTI, and could provide insights for human therapies.[943]

In another NIH-funded study, researchers discovered that levels of the kidney-produced LCN2 molecule were very high in the urine of patients suffering from UTIs and fell as the infection resolved. The kidney cells responsible for making LCN2 were alpha-intercalated cells. Mice lacking these kidney cells were less able to suppress UTIs, possibly providing insights into future directions for understanding human UTIs.[944]

Some UTI-causing *Escherichia coli* (*E. coli*) can influence their ability to cause disease through the regulation of a molecule called α-hemolysin (HlyA), which damages bladder cells by causing holes in the bladder cell membrane. NIH-funded research identified nine bacterial survival genes, including *cus*, a gene that helps *E. coli* survive the toxic effect of copper that the body uses to fight infection.[945,946]

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[941] https://nih-lurn.org/.
[942] Pearce MM, et al. *Am J Obstet Gynecol* 2015;213(3):347.e1-11.PMID: 26210757.
[943] Hannan TJ, et al. *EBioMedicine* 2014;1(1):46-57. PMID: 26125048.
[944] Paragas N, et al. *J Clin Invest* 2014;124(7):2963-76. PMID: 24937428.
[945] Nagamatsu K, et al. *Proc Natl Acad Sci* 2015;112(8):E871-80. PMID: 25675528.
[946] Subashchandrabose S, et al. *Proc Natl Acad Sci* 2014;111(51):18327-32. PMID: 25489107.

UTI-causing *E. coli* were also shown to alter the pH of lysosomes so that they no longer have the ability to degrade the bacteria. The lysosomal membrane protein, called mucolipin TRP channel 3, senses the change in pH and sets in motion a series of events leading affected lysosomes to travel to and fuse with the bladder cell membrane, subsequently expelling the bacteria into the urine.[947]

Improving Treatment and Prevention

Many women develop pelvic organ prolapse as they age, a condition that occurs when the uterus descends into the vagina or when vaginal walls protrude. More than 300,000 surgeries are performed annually in the U.S. for pelvic organ prolapse. Two different vaginal surgical techniques are commonly used, and often women are encouraged to undergo a training therapy before and after surgery to help strengthen pelvic muscles. These techniques—called native tissue repairs—do not use vaginal mesh. NICHD-supported scientists conducted a rigorous randomized controlled clinical trial to compare the effectiveness of the two vaginal surgical techniques and to assess whether adding the therapy helped improve the outcomes of surgery. Two years after surgery, the results showed that neither of the two vaginal surgical techniques was more effective than the other. Moreover, women who added the therapy did not have better outcomes after surgery.[948]

Figure 38. The bladder (blue) of a laboratory mouse infected with *Escherichia coli* (pink), a common cause of UTIs. 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, St. Louis.

To date, the majority of public and private research efforts on LUT problems have focused on management and treatment of severe LUT symptoms. Women bear a disproportionate share of the burden of these symptoms compared to men. NIDDK is spearheading a new research program with an emphasis on symptom prevention, which could benefit the health of a large proportion of women. In FY 2015, NIDDK, with NIA and ORWH, established the Prevention of Lower Urinary tract Symptoms (PLUS) Research Consortium. This multi-center, multidisciplinary consortium will plan, perform, and analyze

[947] Miao Y, et al. *Cell* 2015;161(6):1306-19. PMID: 26027738.
[948] Barber MD, et al. *JAMA* 2014;311(10):1023-34. PMID: 24618964.

research studies necessary to establish the scientific foundation for future prevention–intervention studies for LUT symptoms and conditions in women.

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 chronic and often rare illnesses due in part to an inappropriate immune system response that leads the body to attack its own organs, tissues, and cells. Autoimmune diseases affect more than 23.5 million people in the U.S., with women being affected more than men.[949] The most common autoimmune diseases include systemic lupus erythematosus (SLE or lupus), MS, type 1 diabetes, autoimmune thyroid diseases, myasthenia gravis, scleroderma, rheumatoid arthritis (RA), and inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis. (More information about NIH research on MS and diabetes is available in the Neuroscience and Diabetes sections in Chapter 3). Although treatments are available for many autoimmune diseases, cures have yet to be discovered, and patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, and hospitalization. The social and financial burden of these diseases is immense and includes poor quality of life, high health care costs, and substantial loss of productivity.

Summary of NIH Activities

NIH recognizes that more research is needed to close the gaps in knowledge and reduce the rising impact of autoimmune diseases. NIH is committed to advancing the understanding of how autoimmune diseases develop and to applying results of basic research to improve the health and quality of life of patients affected with these diseases. NIH supports research on the underlying molecular basis and screening, diagnosis, and treatment of autoimmune diseases, as well as identifying emerging autoimmune diseases. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH Institutes, including NIAID, NCATS, NCI, NEI, NHGRI, NHLBI, NIAMS, NIDCR, NIDDK, NIEHS, NIMHD, NLM, and ORWH, conduct and support autoimmune disease research. NIH funding for autoimmune diseases research was $822 million in FY 2014 and $821 million in FY 2015.[950] Following a multi-year portfolio analysis that indicated a downward trend in fundamental immunology grant submissions, including autoimmunity, in FY 2015, NIAID published a program announcement with set-aside funds to promote the submission of grant applications focused on immunological principles.[951]

Molecular Basis of Autoimmune Diseases

Understanding the biological factors leading to autoimmune disease may lead to developing new and more effective treatments for patients. Research conducted by NIH-supported researchers has led to a

[949] https://www.womenshealth.gov/a-z-topics/autoimmune-diseases.
[950] https://report.nih.gov/categorical_spending.aspx.
[951] https://grants.nih.gov/grants/guide/pa-files/PAS-15-055.html.

greater understanding of antigen presentation, immune responses, genetic factors, the role of cell death, risk factors for autoimmune disease, and nonimmune 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. NIAID IRP investigators demonstrated that a normally rare population of atypical NK cells plays a key role in initiating and aggravating lupus in mouse models. These atypical NK cell populations were expanded during chronic activation of the immune system—as occurs in autoimmune diseases such as lupus—and could induce persistent autoimmune disease in transplantation studies. These findings provide valuable information on how lupus progresses, potential biomarkers of disease, and may ultimately identify points in the disease process that can be disrupted through targeted therapeutics.[952]

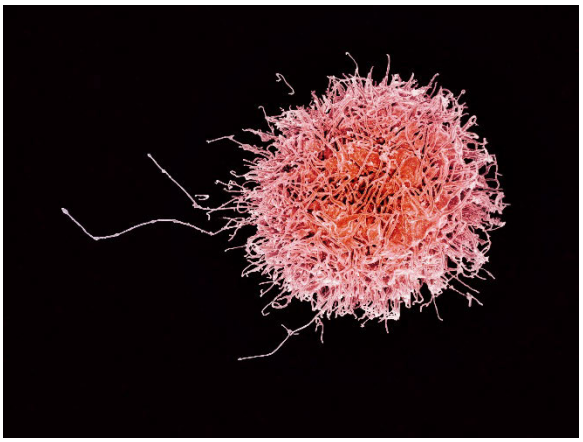

Figure 39. Colorized scanning electron micrograph of a natural killer cell from a human donor. Credit: NIAID.

Another group of NIAID Intramural researchers identified mutations in CTLA-4, an inhibitory receptor found on immune cells, in subjects with severe immune dysregulation. Mechanistic understanding of immune function can help greatly in identifying and developing novel therapies for immune disorders.[953] A third group of NIAID Intramural scientists discovered that dysregulated cytokine signaling in patients with early-onset autoimmunity and lymphoproliferative disease were due to gain-of-function mutations in a protein-signaling pathway. These findings have important implications for understanding immune cell tolerance and the pathogenesis of systemic autoimmunity. The control of lymphocyte (a type of white blood cell) proliferation and tolerance is essential for both host defense and protection against autoimmunity. An improved understanding of the mechanisms that regulate immune tolerance has the potential to improve the treatment of common autoimmune disorders by identifying and then targeting the relevant cellular pathways.[954]

Autoimmune diseases occur in part due to the immune system attacking its own cells. Therefore, it is of interest to also understand why autoantigens are attacked. Dendritic cells are a component of the mammalian immune system that process antigens and place them on their surface for detection by the

[952] Voynova E, et al. *J Immuno.* 2015;195(3):806-9. PMID: 26109646.
[953] Kuehn HS, et al. *Science* 2014;345(6204):1623-7. PMID: 25213377.
[954] Milner JD, et al. *Blood* 2015;125(4):591-9. PMID: 25359994.

T cells, a type of lymphocyte. NIAID IRP investigators demonstrated immune activation induced by increased dendritic cell migration to lymph nodes, a previously unknown effect of antibody binding to antigen. This may occur in SLE, potentially driving the inappropriate localization of autoantigen-bearing DCs.[955] Additionally, T cell receptors (TCR) recognize peptides, small biologically occurring chains, which are presented by molecules on the cell surface of other cells, and use this information to determine *self* versus *non-self*. There are instances where recognition of these complexes can be cross-reactive between similar self and foreign peptides. NIAID-supported researchers showed that cross-reactivity can influence the relevant T cell populations and allow for the development of autoimmunity after infection.[956]

Removing dying, or apoptotic, cells is required to prevent autoimmunity. NIAID IRP investigators demonstrated that the cell surface receptor CD300f mediates the apoptotic cell clearance required for suppression of autoimmunity. Researchers elucidated the mechanisms whereby CD300f recognizes molecules on the surface of apoptotic cells and promotes phagocytosis, or ingestion, by macrophages. The biological consequences of CD300f deficiency in mice were impaired apoptotic cell clearance and a predisposition to development of autoimmune disease.[957] Another group of IRP researchers made significant advances in understanding the mechanisms of immune tolerance (how your immune cells are tolerant to your own tissues and organs) with a focus on the developmental pathways of a specific type of immune cell called regulatory T cells (Tregs). Without Tregs, both mice and humans would die from uncontrolled systemic inflammation and autoimmunity. NIDCR scientists discovered that the development and generation of Tregs in the thymus is driven by programmed cell death. Further research to understand the programmed cell death process could result in more effective and specific immunotherapies for cancer and autoimmune diseases.[958]

Several genetic studies have provided insight into the causes of autoimmune diseases. By analyzing the genomes of thousands of people, scientists funded by NIAMS, NIDCR, and NIAID have uncovered several genes associated with Sjögren's syndrome (SS) that could help researchers develop new strategies to diagnose and treat the condition. By comparing them to roughly 7,000 DNA samples from healthy volunteers, they identified six genes associated with the condition. Some of these genes have been linked to other autoimmune diseases as well, suggesting that they play a broader role in disturbing the immune system. The researchers also confirmed a previously known strong connection between SS and molecules in the *HLA* family, which are crucial for immune function.[959]

Another study shed light on fundamental genes, pathways, and cell types that contribute to RA pathogenesis, and provides empirical evidence that the genetics of RA can provide important information for drug discovery. Using a systematic strategy to integrate disease-associated variants with diverse genomic and biological datasets, scientists conducted a genome-wide association study meta-

[955] Clatworthy MR, et al. *Nat Med* 2014;20(12):1458-63. PMID: 25384086.
[956] Nelson RW, et al. *Immunity* 2015;42(1):95-107. PMID: 25601203.
[957] Tian L, et al. *Nat Commun* 2014;5:3146. PMID: 24477292.
[958] Konkel JE, et al. *Proc Natl Acad Sci USA* 2014;111(4):E465-73. PMID: 24474796.
[959] Lessard CJ, et al. *Nat Genet* 2013;45(11):1284-92. PMID: 24097067.

analysis. They identified biological candidate genes, which were demonstrated to be the targets of approved therapies for RA.[960]

In addition, NIH IRP researchers combed the genome of T cells for regions that are particularly accessible to proteins, a hallmark of DNA segments that carry switches that can control gene activity. They identified several hundred of these regions, and further analysis showed that the switches largely control the activities of genes that encode cytokines and cytokine receptors. These types of molecules are important for T cell function because they enable them to communicate with other cells and to mount an immune response. The researchers' most striking observation was that a large fraction of previously identified genetic alterations associated with RA and other autoimmune diseases localized to these switch regions, suggesting that they play an important role in autoimmunity.[961]

Factors outside of the immune system may also play a role in autoimmunity. For example, a NIAMS-supported advance suggests that the microbiome plays an important role in RA. Researchers compared the gut microbiome of people with new-onset, untreated RA to that of healthy controls, patients with RA who were receiving treatment, and patients with psoriatic arthritis. They found that the bacterium *Prevotella copri* (*P. copri*) was more abundant in patients with new-onset, untreated RA than in the other groups, suggesting that the bacterium contributes to the development of the disease. More extensive studies are needed to determine whether *P. copri* can cause RA, but if so, therapies that target the bacterium could help to prevent the disease or delay its onset.[962]

Similarly, NIDCR IRP scientists have discovered that the gut microbiota plays an important role in preventing adults from developing autoimmune and inflammatory diseases in the skin. Using a mouse model of psoriasis, they found that the depletion and damage of the gut bacterial composition by antibiotic treatment in newborns could increase the susceptibility to psoriasis in later life. Two key findings from this study are that the gut microbiota in early life contribute significantly to health of an adult, and the uncontrolled use of antibiotics, especially in childhood, may have unwanted and even devastating consequences of increasing the susceptibility to autoimmune disease and inflammation in adults.[963]

Furthermore, NIAMS-funded investigators have found that bacterial communities known as biofilms may play a role in development of SLE. The researchers studied a protein, called curli, produced by certain gut bacteria. They found that curli-DNA complexes, present in many common bacterial biofilms, can accelerate SLE pathology in mice that are prone to developing the disease, and can elicit autoimmunity even in normal control mice. The findings shed light on the role of microorganisms in SLE, and suggest that treating underlying infections may benefit people with the disease.[964]

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[960] Kohlhoff KJ, et al. *Nat Chem* 2014;6(1):15-21. PMID: 24345941.
[961] Vahedi G, et al. *Nature* 2015;520(7548):558-62. PMID: 25686607.
[962] Scher JU, et al. *ELife* 2013;2:e01202. PMID: 24192039.
[963] Zanvit P, et al. *Nat Commun* 2015;6:8424. PMID: 26416167.
[964] Gallo PM, et al. *Immunity* 2015;42(6):1171-84. PMID: 26084027.

In another example, experimental observations suggest that alterations in the nervous system might be involved in psoriasis, an autoimmune disease that affects the skin. For example, emotional stress is often coupled with psoriasis exacerbation. Nerve injury and skin denervation (loss of skin nerve connections) are linked to disease remission. A recent study examining the molecular mechanisms by which the nerves are involved in psoriasis showed that certain skin peripheral nerves interact with immune cells to drive inflammation in this condition. Further validation of this model, especially in patients with psoriasis, may open novel avenues for the treatment of inflammatory skin diseases, including psoriasis.[965]

Anerrant immune system is thought to be the primary culprit in RA, but research has shown that cells called fibroblast-like synoviocytes (FLS) also contribute by invading joint cartilage and secreting damaging enzymes and inflammatory molecules. In a NIAMS-funded study, a protein present at high levels in FLS of RA patients was found to regulate the FLS invasiveness. Disrupting such interactions using a decoy fragment of the protein not only decreased the FLS invasiveness in human cells, but also reduced the severity of disease in a mouse model of RA.[966]

Finally, understanding and minimizing exposure to risk factors may lead to a reduction in autoimmune disease diagnoses. For example, exposure to crystalline silica has been linked to increased incidence of autoimmunity, including SLE. Research supported by NIEHS examining the mechanisms underlying this link to autoimmunity have found in an SLE-prone mouse model that the lung serves as a platform for trigging systemic inflammation, which leads to autoimmune responses and kidney glomerulonephritis.[967] Another study, the Twin Sibling study protocol, enrolled more than 200 twins and same-gender (close in age) sibling pairs in which one individual was recently diagnosed with a systemic autoimmune disease (such as juvenile and adult myositis, RA, SLE, or scleroderma), and the other was unaffected. The researchers found evidence to corroborate previous findings associating viral infection with the development of systemic autoimmune disease.[968] Also in FY 2014, NIEHS funded applications to study the role of environmental exposures in the development of autoimmune diseases.[969]

Autoimmune Disease 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, a recent study brings us a step closer to developing biomarkers that can help predict lupus flares. NIAMS-funded researchers compared 52 different soluble molecules in plasma from SLE patients that developed a flare after a baseline assessment and patients that did not. Compared to patients with clinically stable disease, SLE patients with impending flare had higher levels of proinflammatory cytokines and lower levels of regulatory mediators, suggesting that the balance between inflammatory and regulatory

[965] Riol-Blanco L, et al. *Nature* 2014;510(7503):157-61. PMID: 24759321.
[966] Doody KM, et al. *Sci Transl Med.* 2015;7(288):288ra76. PMID: 25995222.
[967] Bates MA, et al. *PLoS One* 2015;10(5):e0125481. PMID: 25978333.
[968] Gan L, et al. *PLoS One* 2015;10(11):e0142486. PMID: 26556803.
[969] https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-13-011.html.

factors is altered before a lupus flare. The results may lead to earlier and more effective treatment or even prevention of flares, and may help optimize therapy for all patients by differentiating those with stable disease from those who might benefit from preventive therapies.[970]

Additionally, scientists have identified low-density granulocytes (LDGs) as a potential biomarker for predicting which patients with the autoimmune disease antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis (AAV) are more likely to respond to treatment. Antibodies against neutrophils, a type of white blood cell, are used in clinical diagnosis of AAV, but there is no reliable method for predicting AAV treatment outcomes. Researchers revealed that the gene expression profile from patients' blood correlates with disease activity and patient response to treatment. Importantly, this study identifies LDGs as a potential biomarker for predicting patients' treatment outcomes.[971]

In another study, researchers found that high doses of fluticasone, a corticosteroid, can safely and effectively induce remission in many people with eosinophilic esophagitis (EoE), a chronic inflammatory disease of the esophagus characterized by high levels of white blood cells (eosinophils). However, some trial participants did not respond to fluticasone even after six months of high-dose treatments, providing evidence that certain people with EoE are steroid-resistant. By analyzing gene expression—the degree to which certain genes are turned on or off—in esophageal tissues, the scientists identified a cluster of genes that may help predict steroid responsiveness. This insight can inform more effective treatments.[972] Additionally, two studies on SS have identified new methods for screening SS patients, leading to more appropriate treatment. Using salivary gland biopsies from SS patients and healthy individuals, NIDCR-supported investigators reported that defective intracellular calcium release plays a critical role in the reduced saliva secretion seen in SS. The study also correlated this disrupted calcium release with an immune system regulating protein called lymphotoxin-alpha, a biomarker for SS disease progression. Together, these findings demonstrate that defects in calcium pathways underlie secretory dysfunction in SS patients and will help identify new targets for effective treatments.[973] The second study demonstrated that immune regulating proteins, specifically interferons, play significant roles in the pathogenesis of autoimmune diseases, including SS. NIDCR-supported investigators found that IFN activity was high in more than 50 percent of SS patients and was associated with a more severe form of the disease. This finding provides a new metric for stratifying SS patients based on IFN status, which will allow for a precision-based approach to identifying individuals that are most likely to respond to anti-IFN treatments.[974]

Accurate screening and diagnosis can minimize future adverse outcomes. Researchers determined that MRI screening can effectively be used to determine whether an RA patient is in remission. As part of a larger clinical trial comparing the effectiveness of different treatment options for patients with RA, a NIAMS-funded study used MRI to help evaluate patient responses to various treatments. Different methods to determine if a patient was in clinical remission were compared to the MRI findings of the

[970] Munroe ME, et al. *Arthritis Rheumatol* 2014;66(7):1888-99. PMID: 24578190.
[971] Grayson PC, et al. *Arthritis Rheumatol* 2015;67(7):1922-32. PMID: 25891759.
[972] Butz BK, et al. *Gastroenterology* 2014;147(2):324-33.e5. PMID: 24768678.
[973] Teos LY, et al. *Sci Rep* 2015;5:13953. PMID:26365984.
[974] Hall JC, et al. *Arthritis Rheumatol* 2015;67(9):2437-46. PMID: 25988820.

patient's wrist. Despite being a small study, it was observed that even though patients appeared to be in remission clinically, there was still ongoing evidence of damage as seen by MRI. These results suggest that the goal of withdrawing, or temporarily stopping, therapy for patients who otherwise appear to be in remission needs to be reconsidered until information from other studies clarifies this clinically important issue.[975]

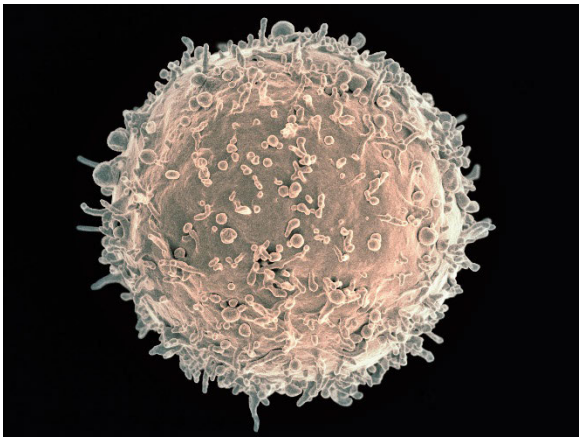

Figure 40. Colorized scanning electron micrograph of a B cell from a human donor. Credit: NIAID.

Several drugs are being tested to determine whether they can be effectively used as first-line or secondary treatments for autoimmune diseases. NIAID IRP investigators have demonstrated that patients with an autoimmune syndrome caused by lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency showed dramatic improvement in response to abatacept therapy. Abatacept is a drug that interferes with T-cell activity and is used to treat autoimmune diseases. The investigators showed that abatacept therapy targeting CTLA-4, a protein receptor that helps regulate the immune system, was highly effective in reversing life-threatening autoimmune disease in LRBA-deficient patients. These findings elucidate a mechanism for CTLA-4's control of immune responses and suggest therapies for diseases involving the CTLA-4 pathway.[976] Furthermore, alopecia areata (AA) is an autoimmune disease where the immune system attacks hair follicles, leading to hair loss. NIAMS-funded scientists demonstrated that patients with AA could be treated with the FDA-approved drug, ruxolitinib, and experience near-complete hair regrowth within three to five months of treatment. The research with humans built on the scientists' previous work using a mouse model to study AA.[977] In addition, treatment with fresolimumab, a new but unapproved drug that blocks all forms of transforming growth factor (TGF)–beta, resulted in a decrease in skin fibrosis in a group of 15 patients with early diffuse cutaneous systemic sclerosis (SSc). Patients receiving the drug showed a rapid decline in the expression of several TGF-beta–regulated genes in skin, as well as improvement in the main clinical measure of skin fibrosis, the modified Rodnan skin score. The results provide direct support for the role of TGF-beta as a mediator of skin fibrosis in humans and may be applicable to the treatment of fibrosis in other organs (e.g., lungs) in people with SSc. The findings also show promise for the development of biomarker

[975] Ranganath VK, et al. *Arthritis Care Res (Hoboken)* 2015;67(7):929-39. PMID: 25581612.
[976] Lo B, et al. *Science* 2015;349(6246):436-40. PMID: 26206937.
[977] Xing L, et al. *Nat Med* 2014;20(9):1043-9. PMID: 25129481.

surrogate outcome measures, such as changes in gene expression that could allow for more rapid detection of potential therapeutic effects in clinical trials.[978]

Three-year outcomes from another ongoing clinical trial suggest that high-dose immunosuppressive therapy followed by transplantation of a person's own blood-forming stem cells may induce sustained remission in some people with relapsing-remitting multiple sclerosis (RRMS). RRMS is the most common form of MS, a progressive autoimmune disease in which the immune system attacks the brain and spinal cord. The trial is funded by NIAID and conducted by the NIAID-funded Immune Tolerance Network.[979,980]

NEI investigators are testing prospective treatments for uveitis, a serious inflammation of the eye that causes vision loss, in a preclinical model. They have discovered an immune cell type that suppressed inflammation associated with autoimmune uveitis. The immune cell produces a protein called interleukin-35, which prevents the progression of uveitis in a mouse model of the disease. This finding could offer an alternative to steroids, which are the mainstay of uveitis treatment, but are linked with complications such as glaucoma and cataract. It might also offer treatment of other autoimmune diseases and transplant rejection.[981]

In another noteworthy development, 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 in RA and lupus (AMP-RA/SLE) 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. The AMP –RA/SLE, implemented by a national research network, is analyzing the interplay among biological pathways, including at the single-cell level, in tissues of patients with RA and SLE. The goal is to integrate data from multiple genome-wide approaches to generate a comprehensive understanding of the mechanisms of tissue damage in RA and lupus.[982]

In February 2015, to facilitate the translation of recent discoveries in scleroderma research to clinical applications, NIAMS held a roundtable on advancing potential drugs for scleroderma to patient care. The meeting brought together representatives from academic institutions, regulatory and funding agencies, patient organizations, and industry to exchange information, ideas, and perspectives about the status of scleroderma research leading to drug development, opportunities and obstacles to advancing the evaluation of new therapeutic targets, and potential approaches to move candidate drugs into robust clinical trials and, eventually, clinical care.[983]

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[978] Rice LM, et al. *J Clin Invest* 2015;125(7):2795-807. PMID: 26098215.
[979] http://www.niaid.nih.gov/news/newsreleases/2014/Pages/HALT-MS.aspx.
[980] Nash RA, et al. *JAMA Neurol* 2015;72(2):159-69. PMID: 25546364.
[981] Wang RX, et al. *Nat Med* 2014;20(6):633-41. PMID: 24743305.
[982] https://www.niams.nih.gov/Funding/Funded_Research/AMP_RA_lupus/default.asp.
[983] https://www.niams.nih.gov/News_and_Events/Meetings_and_Events/Roundtables/2015/scleroderma.asp.

Infectious Diseases and Biodefense

Threats to public health change continually as new pathogens emerge in nature and as familiar microbes reemerge with new properties or in unusual settings. In 2015, infectious diseases and maternal, neonatal, and nutrition conditions collectively caused approximately 20 percent of all deaths worldwide and accounted for approximately 30 percent of disability-adjusted life years.[984] Within the World Health Organization (WHO)–defined African Region, 56 percent of deaths were due to such conditions.[985] Three of the top 10 causes of death worldwide are infectious diseases: lower respiratory infections, diarrheal diseases, and TB. In low-income economies, five of the top 10 causes of death are infectious diseases as HIV/AIDS and malaria are also significant contributors to death in developing countries.[986] In addition to naturally occurring infectious diseases, deliberate release of pathogenic agents such as anthrax or smallpox could cause large-scale disruption and devastation, necessitating NIH-supported research in biodefense.

Summary of NIH Activities

NIH supports and conducts research on major infectious diseases, including HIV/AIDS, TB, malaria, viral hepatitis, and emerging and re-emerging infectious diseases, as well as such related concerns as antimicrobial resistance (AMR), Ebola, and influenza. NIH-supported research on infectious and emerging diseases and biodefense covers a wide array of research areas including basic immunology research and applied research in prevention, diagnosis, and treatment. For example, investigators in NIAID IRP identified a special population of immune system cells, called dendritic cells, that process and identify antigens, the molecules that produce an immune response. This newly discovered population of dendritic cells resides directly in the lymph nodes, where they are in position to initiate a rapid immune response.[987] Additionally, in 2014, NIAID awarded seven contracts for the discovery of new vaccine adjuvants.[988] Adjuvants are substances that are formulated as part of a vaccine to enhance their protective ability. Currently, there are only three FDA-approved adjuvants in use. The discovery and characterization of new adjuvants will help NIAID reach the goals described in the Strategic Plan for Research on Vaccine Adjuvants.[989]

Research on infectious diseases and biodefense is primarily conducted and supported by NIAID. However, other NIH entities, including NIH CC, NIDCR, NIDA, NIDCD, NIDDK, NICHD, NIEHS, NIMH, FIC, NCATS, and NLM, also support research in this area, as do OAR and the Common Fund within NIH OD. NIH funding for infectious diseases research was $5,002 million in FY 2014 and $5,032 million in FY

[984] http://ghdx.healthdata.org/gbd-results-tool.
[985] http://who.int/gho/mortality_burden_disease/en/.
[986] http://www.who.int/mediacentre/factsheets/fs310/en/index1.html.
[987] Gerner MY, et al. *Immunity* 2015; 42(1):172-85. PMID: 25607462.
[988] https://www.niaid.nih.gov/news-events/nih-awards-seven-new-vaccine-adjuvant-discovery-contracts.
[989] https://www.niaid.nih.gov/sites/default/files/NIAID-StrategicPlanVaccineAdjuvants.pdf.

2015.[990] NIH funding for biodefense research was $1,746 million in FY 2014 and $1,736 million in FY 2015.[991]

Major Infectious Diseases

Major infectious diseases such as HIV/AIDs, malaria, TB, and viral hepatitis are significant causes of death around the world. Worldwide in 2015, HIV caused 1.2 million deaths, TB killed 1.1 million, and viral hepatitis infections caused over 100,000 deaths.[992] Malaria remains a serious problem, especially in low-income economies, where it caused more than 700,000 deaths in 2015. In addition to the previously mentioned diseases, NIH supported research on other infectious diseases including:

- *Otitis media (OM):* NIDCD-supported scientists have repurposed a drug that has long been used to treat stroke as a novel treatment for OM, or middle ear infection. They found that topical administration of the drug vinpocetine suppressed inflammation and the overproduction of mucous cause by bacterial infection. This discovery may lead to a nonantibiotic agent to combat OM with minimal side effects.[993]
- *Epstein-Barr virus (EBV):* NIAID Intramural scientists have capitalized on emerging nanoparticle technology to develop a candidate vaccine for EBV, which is associated with multiple human diseases including infectious mononucleosis and cancer. The researchers designed a nanoparticle structure to focus the immune response on a specific region and structure of an EBV surface protein. The vaccine produced a robust response in both mice and nonhuman primates, and the response was significantly greater than previously developed vaccines. This new design strategy may be useful in creating or redesigning vaccines against pathogens for which it has been difficult to induce immunity.[994]
- *Respiratory syncytial virus (RSV):* RSV infection is the most common cause of lower respiratory tract infections among young children worldwide. RSV infection in children under the age of 2 leads to 75,000 to 125,000 hospitalizations each year. Scientists in the NIAID IRP, and in universities and medical research centers across the U.S., work together to translate this knowledge into new, safe, and effective ways to treat and prevent RSV. In 2015, NIAID Intramural researchers initiated a new study that will expose healthy adult volunteers to RSV. The information gained from this trial will help researchers develop and test future antivirals and vaccines to combat the virus.[995] Additionally, NIAID Intramural researchers and collaborators at the Johns Hopkins Bloomberg School of Public Health developed an attenuated

[990] https://report.nih.gov/categorical_spending.aspx.
[991] Reporting for this category does not follow the standard Research, Condition, and Disease Categorization (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 does not include nonproject 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/topics/biodefenserelated/pages/default.aspx.
[992] http://ghdx.healthdata.org/gbd-results-tool.
[993] Lee JY, et al. *J. Immunol* 2015;194(12)5990-8. PMID: 25972475.
[994] Kanekiyo M, et al. *Cell* 2016;162(5):1090-100. PMID: 26279189.
[995] https://www.niaid.nih.gov/news-events/nih-launches-human-rsv-study.

RSV vaccine with improved correlates of protection in children. The new vaccine demonstrated an improved antibody response in vaccinated children. Followup of the children provided evidence suggesting that the vaccine provided immunity to RSV.[996]

- **Sexually transmitted diseases (STDs):** Chlamydia is a common STD caused by infection with *Chlamydia trachomatis*. Untreated, it can result in serious health consequences in men and women. A NIAID-funded study tested a vaccine that showed promise in conferring protection against chlamydia. Mice were vaccinated with inactivated *C. trachomatis* attached to a nanoparticle that contained an adjuvant. When the vaccine was administered to female animals via mucosal routes and targeted to the proper population of cells, the mice were protected against infection.[997] Studies on HPV are included in the Cancer subsection of Chapter 3, due to the connection between HPV and cervical cancer.

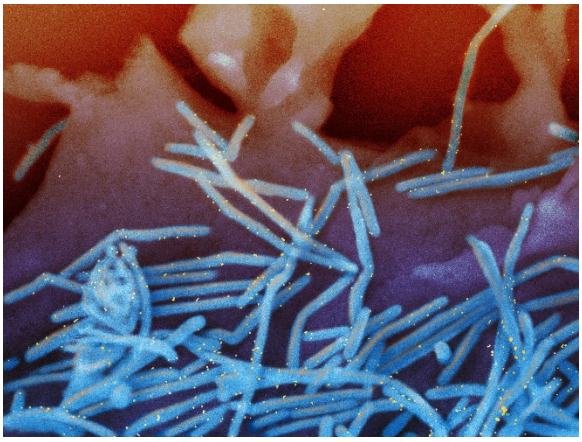

Figure 41. Scanning electron micrograph of human respiratory syncytial virus (RSV) virions (blue) and labeled with anti-RSV F protein/gold antibodies (yellow). Credit: NIAID.

HIV/AIDS

The number of deaths from HIV/AIDS in the U.S. has fallen dramatically; in 1990 there were approximately 27,000 deaths, compared with approximately 7,500 in 2015. However, there are still more than 350,000 disability-adjusted life years lost due to the disease.[998] NIH has a robust HIV portfolio that includes research on the basic mechanisms of HIV infection, increasing prevention through pre-exposure prophylaxis (PrEP) or vaccination, improving treatments, reducing mother-to-child transmission of HIV, treating infants and children, and managing secondary complications. NIH funding for HIV/AIDS research was $2,978 million in FY 2014 and $3,000 million in FY 2015.[999]

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[996] Karron RA, et al. *Sci Transl Med* 2015;312(7):312ra175. PMID: 26537255.
[997] Stary G, et al. *Science* 2015;348(6241): aaa8205. PMID: 26089520.
[998] http://ghdx.healthdata.org/gbd-results-tool.
[999] The total for AIDS research includes both extramural and intramural research (including research management and support, Management Fund, and Service & Supply Fund), buildings and facilities, research training, and program evaluation, as well as research on the many HIV-associated co-infections and co-morbidities, including TB, hepatitis C, and HIV-associated cancers. It also includes all of the basic science underlying this research. Other

Preventing HIV Infection

HIV is an incurable illness, necessitating significant investment in methods to prevent transmission of HIV from infected individuals. There are three major approaches for preventing HIV infection. First, PrEP is recommended as a prevention choice for people at substantial risk for HIV exposure. This recommendation is based on clinical trial findings that the antiretroviral (ARV) drug Truvada (tenofovir and emtricitabine) is useful in preventing transmission of HIV. NIH supports research verifying the efficacy of PrEP and developing appropriate treatment regimens. A second approach is treating the infected individual with antiretroviral therapy (ART) early in the disease progression to protect an uninfected sexual partner. NIH continues to fund research to develop and test vaccines to prevent HIV infection, a third approach.

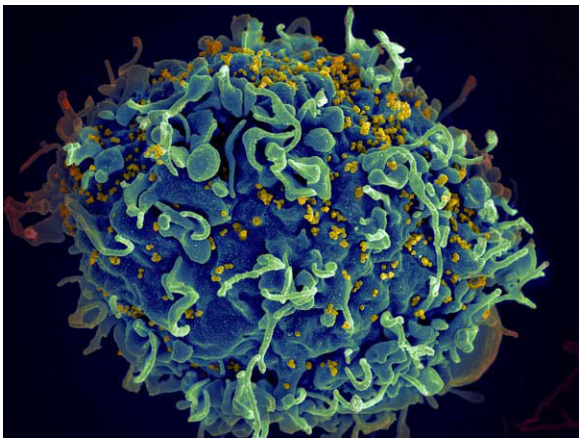

Figure 42. Human T cell (blue) under attack by HIV (yellow). Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, NIAID.

Several studies converged to highlight the effectiveness of PrEP in preventing the acquisition of HIV among high-risk population. One study conducted at Kaiser Permanente in San Francisco involved more than 600 high-risk individuals, most of whom were men who have sex with men (MSM). These individuals were healthy at the time of enrollment and were placed on a daily regimen of Truvada. Referrals for and initiation of PrEP for HIV infection increased dramatically in a large clinical practice setting since 2012. Despite high rates of sexually transmitted infections (STIs) among PrEP users and reported decreases in condom use in a subset, there were no new HIV infections in this population. One concern with the PrEP approach is adherence to the treatment plan. The U.S. PrEP Demonstration Project, which assessed PrEP delivery and use by MSM and transgender women (TGW), reported high PrEP adherence, with 65 percent of participants whose drug levels were tested showing levels consistent with at least four doses per week at all visits. Low HIV incidence was also observed among this cohort at high ongoing risk for HIV. At the same time, the study showed that STIs were common among the participants, though STIs did not increase over the course of the study.[1000] Furthermore, the NIAID-supported Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking (ADAPT) Study,

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RCDC categories are not reported this way; thus the total for 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/hivaids/.

[1000] Volk JE, et al. *Clin Infect Dis* 2015;61(10):1601-3. PMID: 26334052.

which enrolled women in South Africa and Black MSM and TGW in New York and Thailand, demonstrated that most study participants had higher coverage of sex events and better adherence to PrEP when they took ARV daily as opposed to nondaily alternatives.[1001] NIAID is also supporting research examining the safety and effectiveness of alternative, long-acting delivery systems for PrEP for HIV, such as injectable PrEP and the use of different agents for this purpose. The HPTN 076 trial is a Phase II study to evaluate the safety and acceptability of a long-acting injectable form of the FDA-approved antiretroviral drug rilpivirine. A similar trial, HPTN 077, is a Phase II trial that is evaluating the safety, pharmacokinetics, and acceptability of an investigational antiretroviral drug that is being simultaneously developed for both HIV treatment and prevention in oral and injectable form.[1002]

ART can also be taken by the infected partner to prevent infection in the uninfected partner in HIV-discordant couples, couples where one partner is HIV-positive and the other is not. In 2015, NIAID announced the follow-up results of a study to test the efficacy of ART in preventing HIV transmission among HIV-discordant couples. This method is durable and no HIV transmissions were observed when the HIV-infected participant was stably suppressed on ART. The study investigators previously reported a breakthrough: Starting HIV treatment early, when the immune system is relatively healthy, reduced the risk of sexually transmitting the virus to an uninfected partner by 96 percent over 18 months. Based on additional data gathered since 2011, the study unequivocally demonstrated the enduring power of HIV-controlling ART to greatly reduce sexual transmission of the virus.[1003] NIAID is also continuing to support the Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) study, which is examining the impact of a combination prevention package featuring immediate ART (versus waiting until CD4 levels decline, according to current national guidelines) and educational and behavioral interventions on population-level HIV incidence in Zambia and South Africa. The PopART study, which began in 2013, is building on the results of a landmark trial that found that HIV-infected individuals who start treatment early, when their immune systems are relatively healthy, dramatically reduce the risk of transmitting the virus to their heterosexual partners.[1004]

NIH supports HIV vaccine research from basic understanding of the components of HIV-1, the most widespread type of HIV worldwide, to clinical trials testing the efficacy and safety of vaccines. Broadly neutralizing antibodies (bNAbs), antibodies that can neutralize multiple strains of HIV-1, have been found in the blood of HIV patients who naturally control progression of the disease, so bNAbs are of particular interest for HIV vaccine development. NIAID researchers studied serial blood samples donated over a roughly two-year period by an HIV-infected South African individual who developed a powerful bNAb response to HIV. The scientists determined that this potent HIV bNAb arose through the cooperative effects of two different B-cell lineages, the immune cells responsible for producing

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[1001] https://www.niaid.nih.gov/news-events/young-south-african-women-can-adhere-daily-prep-regimen-hiv-prevention-study-finds.
[1002] https://www.niaid.nih.gov/news-events/nih-supported-clinical-trials-evaluate-long-acting-injectable-antiretroviral-drugs.
[1003] https://www.niaid.nih.gov/news-events/hiv-control-through-treatment-durably-prevents-heterosexual-transmission-virus.
[1004] https://www.niaid.nih.gov/news-events/study-evaluates-population-wide-testing-early-treatment-hiv-prevention.

antibodies. These findings suggest that traditional vaccination strategies to induce a single B-cell lineage may not be effective for producing HIV bNAbs. Because more than one B-cell lineage may be involved, researchers may need to map multiple bNAb lineages to design an effective vaccination strategy and induce potent anti-HIV antibodies.[1005]

Multiple NIAID-supported animal studies are testing experimental vaccines that induce bNAbs against HIV and have shown promising results in both rabbits and nonhuman primates. In one study, researchers demonstrated that a laboratory-designed molecular complex can stimulate rabbits and monkeys to produce powerful bNAbs against a tough-to-neutralize HIV strain. The complex is similar to the part of HIV that binds to cells—a structure that has been difficult to copy as the kind of stand-alone molecule that an HIV vaccine potentially would need.[1006,1007] NIAID-funded scientists also took the first step toward confirming the prevailing hypothesis of how an HIV vaccine will need to be designed to elicit antibodies that stop a wide range of HIV strains from infecting human cells. The researchers demonstrated in genetically modified mice that an HIV vaccine regimen likely would need to expose the immune system to one type of protein to elicit a nascent antibody with the potential to be broadly neutralizing, and then present another type of protein later on to coax a more mature form of the antibody toward final development.[1008,1009]

The NIAID Vaccine Research Center (VRC) has made progress in helping to elucidate different facets involved in vaccine development for HIV. VRC has successfully sequenced genes coding for the heavy and lights chains (the basic structural units) of known bNAbs, characterized the evolutionary relationships of bNAbs, and identified a novel, non–self-reactive bNAb.[1010,1011] VRC has also undertaken several preclinical endeavors to develop an HIV vaccine. In 2010, VRC researchers identified two naturally occurring bNAbs, VRC01 and VRC02, in the blood of an infected individual. Since then, they have identified a more potent version of VRC01 (VRC07-523LS) and a variant with a longer half-life (VRC01-LS). VRC researchers are also evaluating a potent, nonautoreactive bNAb (10e8) and hypothesize that VRC07-523LS and 10e8 will be useful in the development of future studies.

Based on the modest protection demonstrated by the RV144 vaccine regimen, a vaccine that was tested in Thailand by the U.S. Military HIV Research Program, NIAID launched the HVTN 100 study in 2015. This Phase I/II clinical trial was conducted in South Africa and aimed to evaluate an investigational HIV vaccine regimen (a canary pox-based vaccine called ALVAC-HIV and an HIV surface protein vaccine) that was designed to improve upon the efficacy of the RV144 regimen. Results from this study will help determine whether the vaccine regimen will be evaluated in a follow-up randomized controlled efficacy

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[1005] Gao F, et al. *Cell* 2014;158(3):481-91. PMID: 25065977.
[1006] https://www.niaid.nih.gov/news-events/niaid-funded-hiv-vaccine-research-generates-key-antibodies-animal-models.
[1007] Jardine JG, et al. *Science* 2016;349(6244):156-61. PMID: 26089355.
[1008] https://www.niaid.nih.gov/news-events/niaid-funded-hiv-vaccine-research-generates-key-antibodies-animal-models.
[1009] Dosenovic P, et al. *Cell* 2015;161(7):1505-15. PMID: 26091035.
[1010] Zhu J, et al. *Proc Natl Acad Sci USA* 2013;110(43):E4088-97. PMID: 24106303.
[1011] Lacerda M, et al. *Virol J* 2013;10:347. PMID: 24295501.

study known as HVTN 702.[1012] The HVTN 100 regimen will require each participant to receive eight vaccinations for full immunity. To minimize the problem with adherence to dosing regimens, NIAID-supported researchers investigated whether injections of a long-acting drug, called GSK744, could prevent HIV infection in a nonhuman primate model of HIV. The researchers found that animals who received two injections of the experimental drug four weeks apart were completely protected from infection with SHIV, a laboratory-generated monkey virus that mimics human HIV infection. Even a single drug dose could prevent infection after up to 10 successive exposures to SHIV. These findings suggest that GSK744 could be a potent and effective anti-HIV preventive intervention. The drug is on track for safety and efficacy trials in the HIV Prevention Trials Network as a potential HIV preventive strategy for individuals at high risk of contracting HIV.[1013]

Improving HIV Treatment

NIH continues to support research to improve treatments for individuals living with HIV. NIH-supported research efforts include understanding the molecular basis of HIV, targeting the viral reservoir (the places or populations that harbor the virus), developing therapeutic vaccinations, increasing likelihood of treatment adherence, and conducting epidemiological studies to improve healthcare. The revised Martin Delaney Collaboratories for HIV Cure Research program is designed to address the problem of HIV persistence in HIV-infected persons treated with suppressive antiretroviral drug regimens by fostering dynamic collaboration among academia, industry, government, and community. The overall goal of the program is to develop strategies to achieve either eradication of HIV infection from the body or a functional cure, defined as sustained viral remission following cessation of antiretroviral therapy.[1014]

Understanding the molecular basis of HIV can lead to novel insights resulting in new therapies for HIV. HIV targets specific white blood cells, CD4+ T cells, by using two different cell-surface receptors, R5 and X4. Almost all HIV infections initially use the R5 receptor to enter the CD4 cell. However, in about half of HIV patients, the virus will eventually switch and begin to use the X4 receptor. This switch is usually associated with worsening disease in the patient, and the switch renders the anti-HIV drugs targeted at the R5 receptor less effective. To pinpoint how this receptor switch happens, NICHD-supported scientists isolated two closely related parts of the genetic code of the HIV virus. These two locations signaled different receptors, influenced by slight genetic changes affecting other locations on the virus. The scientists hope that this discovery may help scientists better predict, and potentially counter, HIV's ability to escape antiretroviral drugs.[1015] Additionally, an international group of researchers identified genes that disable HIV-1, suggesting a promising new strategy for battling the virus that causes AIDS. In their two studies, the scientists found that host cell membrane proteins, SERINC5 and SERINC3, significantly reduce the virulence of HIV-1 by blocking the ability of the virus to infect new cells.[1016,1017]

[1012] https://www.niaid.nih.gov/news-events/nih-sponsored-hiv-vaccine-trial-launches-south-africa.
[1013] Andrews CD, et al. *Science* 2014;343(6175):1151-4. PMID: 24594934.
[1014] http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-15-029.html.
[1015] Lombardi F, et al. *PLoS One* 2015;10(6):e0128116. PMID 26083631.
[1016] Usami Y, et al. *Nature* 2015; 526(7572):218-23. PMID: 26416733.
[1017] Rosa A, et al. *Nature* 2015; 526(7572):212-7. PMID: 26416734.

Another promising approach for treating HIV is targeting the HIV reservoir, specifically the latent HIV reservoir. NIAID has launched a number of cure-related scientific programs that aim to address the HIV reservoir. One example is Immune-Based Antiviral Products for Suppression/Elimination of HIV-1, which will provide the resources needed to develop discoveries identified from other NIAID-funded basic science efforts or therapeutic vaccines from biotechnology companies and foundation consortia.[1018] Furthermore, through the Pilot Clinical Trials to Eliminate the Latent HIV Reservoir program, which was initiated in October 2013, NIAID funded two studies in 2015 to evaluate interventions aimed at eliminating latently infected cells. One study will combine two agents that were observed to have an effect on the HIV-1 reservoir in 4 of 15 Danish study subjects on ART. The second pilot trial will combine a different latency-reversing agent with a vaccine prepared from the patient's own immune cells.[1019]

A NIAID-funded study demonstrated that HIV remains active as infected cells transition to rest, suggesting that the two processes are independent, and that HIV, not the host cell, controls virus replication. In another NIAID-supported study, researchers found that periods of latency in mucosal tissue benefitted the virus overall, which likely allows HIV to survive and spread to other tissues. These findings may explain why HIV cure strategies to awaken cells in the latent reservoir have not thus far succeeded.[1020,1021] A team of NIAID-supported scientists examined the ability of three types of latency-reversing agents, including a group of drugs called HDAC inhibitors, to awaken dormant reservoirs of HIV in CD4+ T cells from people infected with HIV. The team found that HDAC inhibitors and other compounds they hoped would awaken dormant reservoirs of HIV inside resting CD4+ T cells failed to do so in laboratory tests of white blood cells taken directly from HIV-infected patients. The study results challenge the idea that a single latency-reversing agent can activate the HIV hiding in cells of patients whose viral load is essentially undetectable via blood tests.[1022] Another team of NIH-sponsored scientists developed a protein that awakens resting immune cells infected with HIV and facilitates their destruction in laboratory studies. The protein potentially could contribute to a cure for HIV infection by helping deplete the reservoir of long-lived, latently HIV-infected cells that can start making the virus when a person stops taking anti-HIV drugs.[1023]

Another approach for effectively treating HIV is the use of therapeutic vaccines. Scientists found that for those who started combination ART within three months of infection, most of the HIV-infected CD4+ T cells in the viral reservoirs were sensitive to detection by killer T cells, the immune cells that seek and destroy infected cells. By contrast, nearly all of the HIV that infected CD4+ T cells in the reservoirs of the late-treatment group had developed mutations that enabled the infected CD4+ T cells to escape detection by killer T cells. These results suggest that a therapeutic vaccine that boosts the T-cell response to HIV could be part of a strategy for curing chronic HIV infection.[1024] Alternatively, the development of potent HIV bNAbs that can prevent infection and suppress viremia is a critical area of

[1018] https://grants.nih.gov/grants/guide/notice-files/NOT-AI-15-046.html.
[1019] http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-13-055.html.
[1020] Rouzine IM, et al. *Cell* 2015;160(5):1002-12. PMID: 25723173.
[1021] Razooky BS, et al. *Cell* 2015;160(5):990-1001. PMID: 25723172.
[1022] Bullen CK, et al. *Nat Med* 2014;20(4):425-9. PMID 24658076.
[1023] Pegu A, et al. *Nat Commun* 2015;6:8447. PMID: 26485194.
[1024] Deng K, et al. *Nature* 2015;517(7534):381-5. PMID: 25561180.

HIV/AIDS research. In a Phase I study, NIAID-funded researchers demonstrated that a single infusion of 3BNC117, an experimental anti-HIV antibody, was safe and resulted in significantly decreased HIV levels that persisted for as long as 28 days in HIV-infected individuals. These results provide further evidence that immunotherapy should be explored as a new modality for HIV prevention, therapy, and cure.[1025] Another group of NIAID-funded scientists developed an antibody-like molecule, known as eCD4-Ig, which could not only provide effective long-term control of chronic HIV infection, but also prevent HIV infection from occurring in the first place. NIAID-supported researchers are also investigating how specifically designed proteins can stimulate the body's production of certain immune cells (B cells) that produce these antibodies.[1026]

Adherence to dosing regimens is a critical issue for both HIV treatment and prevention. Developing new approaches for eliminating or reducing the impact of individual adherence could increase the efficacy of treatment strategies and help prevent HIV transmission. In 2015, NIAID created the Sustained Release of Antivirals for Treatment and Prevention of HIV program, which aims to stimulate the high-risk research needed to develop new and innovative sustained-release antiviral strategies for treatment of HIV disease or the prevention of HIV transmission and acquisition.[1027]

Several epidemiological studies supported by NIH led to a greater understanding of HIV transmission, diagnosis, and treatment. The Multicenter AIDS Cohort Study (MACS), which began in 1984, is the longest-running HIV cohort study in the world, and continues to elucidate the natural and treated history of HIV infection in MSM. The study prospectively follows thousands of homosexual and bisexual men (HIV-infected and HIV uninfected, but at risk) across multiple sites. The MACS has contributed significantly to the scientific understanding of HIV, AIDS, and the effects of antiretroviral therapy through more than 1,000 publications, many of which have guided public health policy and the clinical care of people with HIV.[1028] The Women's Interagency HIV Study (WIHS), which began in 1993, is the largest and longest-running study to investigate the impact of HIV on women. The study has helped define how best to treat HIV-infected women in the U.S. and globally. The WIHS has enrolled more than 4,100 women who were HIV infected or at risk for acquiring HIV, and has published approximately 600 scientific papers. Another rich resource, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium is composed of seven regional databases around the world. IeDEA has contributed substantially to the effort to evaluate and describe the roll-out of therapy around the world, define outcomes for adult and pediatric patients, evaluate the success of programs in care and treatment delivery, define new approaches to managing care in limited resources settings, and describe the epidemiology of cancer in HIV-infected persons around the world. Because of its large size, its commitment to data quality, and novel analytical approaches, IeDEA is able to conduct extensive research to document the use of therapy and changes in the clinical state of HIV globally.

[1025] Caskey M, et al. *Nature* 2015;522(7557):487-91. PMID: 25855300.
[1026] https://www.niaid.nih.gov/news-events/nih-funded-scientists-create-potential-long-acting-hiv-therapeutic.
[1027] http://grants.nih.gov/grants/guide/pa-files/PAR-13-349.html.
[1028] https://statepi.jhsph.edu/macs/macs.html.

Internationally, IeDEA has been a leader in implementation science research and has documented successes and challenges globally in the battle against HIV/AIDS.[1029]

As discussed in Chapter 2, dissemination of knowledge gleaned from biomedical research is key to successful intervention. During FY 2014 and 2015, NLM updated and released two AIDS information mobile health tools for both iOS and Android platforms to improve access to HIV/AIDS information at the point of care. The *AIDSinfo Drug* app was also released, which provides information on more than 100 HIV-related, FDA-approved and investigational drugs. The AIDS glossary was expanded with new terms and the addition of images to improve understanding of the terms and was released on the web, in print, and as a mobile version. In addition, NLM introduced *AIDSource*,[1030] a web portal for HIV/AIDS information. The mobile-optimized website offers access to a comprehensive collection of HIV/AIDS-related information resources from federal and non-federal sources. Resources included on the *AIDSource* website are organized by both topic of interest and audience, and information is available in English and Spanish.

Preventing Mother-to-Child Transmission of HIV and Treatment in Children

The vast majority of all HIV-infected infants and children acquire the virus from their mothers before or during birth or through breastfeeding. Most mother-to-child-transmission (MTCT) occurs late in pregnancy or during birth. Without intervention, transmission rates from mother to child range from 15 to 45 percent. However with effective intervention, this rate is reduced to below 5 percent.[1031] NIH is conducting studies on effective interventions to prevent MTCT of HIV and treat young children with HIV.

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group, cosponsored by NIAID, NICHD, and NIMH, is conducting a large, multinational clinical trial to determine how best to reduce the risk of HIV transmission from infected pregnant women to their babies during pregnancy and breastfeeding, while preserving the health of these children and their mothers. The study found that for HIV-infected women in good immune health, taking a three-drug regimen during pregnancy prevents MTCT more effectively than taking one drug during pregnancy, another during labor, and two more after giving birth. The findings were reported during a scheduled interim review by the Data and Safety Monitoring Board, and support the recommendation by WHO and most countries to provide a three-drug regimen to all pregnant women with HIV infection.[1032] Furthermore, VRC is also evaluating the VRC01 antibody to prepare for the potential design of trials for the prevention of MTCT.

Effecting durable remission or cure of HIV in infants and children would provide significant benefits to children, families, and overburdened treatment programs. Greater understanding of the mechanisms by

[1029] http://www.iedea.org/.
[1030] https://aids.nlm.nih.gov/.
[1031] http://www.who.int/hiv/topics/mtct/en/.
[1032] https://www.niaid.nih.gov/news-events/nih-sponsored-study-identifies-superior-drug-regimen-preventing-mother-child-hiv.

which HIV-1[1033] alters developmental changes in infant immunity and how this in turn affects the natural history of HIV-1 in this unique population may lead to remission strategies that can reduce the burden of HIV disease in children. In 2015, NIAID and NICHD created a new initiative, Understanding HIV Persistence in Infants, to stimulate research on the pathogenesis of perinatal HIV-1 infection by elucidating HIV-1 immune responses in the setting of the infant's evolving immune system and the mechanisms by which latent viral reservoirs are established and maintained. The goal is to gain knowledge to be used in future development of strategies to induce HIV-1 remission.[1034]

In 2013, NIAID-supported investigators described an infant, known as the "Mississippi Baby," who received ART 30 hours after birth and continued therapy through 18 months of age, at which point several treatments were missed. Strikingly, after 5 months without treatment, she had undetectable levels of HIV-1 plasma RNA and maintained remission through 46 months of age, without ART treatment. She eventually experienced viral rebound; however, such a prolonged period off ART is unprecedented in children and serves as the basis for ongoing NIAID HIV research focused on very early ART and sustained HIV remission.[1035] In 2015, NIAID launched the Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission study to evaluate whether initiation of combination ART within the first 48 hours of birth can control viral replication in HIV-infected children and whether HIV remission can be sustained for at least 48 weeks in infants who stop combination ART. The trial will enroll up to 472 babies and their HIV-infected mothers in at least nine countries in Africa and North and South America.[1036] Also, NICHD-supported researchers recently demonstrated that HIV-infected children exposed in the womb to nevirapine, a drug used to prevent MTCT, can safely and effectively transition to efavirenz, a similar drug recommended for older children and adults. Switching children to efavirenz offers several advantages, including once-daily dosing, easier storage, better taste, and lower cost.[1037]

Managing Opportunistic Infections and Comorbidity

Individuals with healthy immune systems can be exposed to infectious microbes without showing a reaction. However, exposure in individuals with weakened immune systems, including those with HIV/AIDS, can cause serious illness. Understanding the molecular basis of these opportunistic infections (OIs) will be critical for long-term treatment of HIV/AIDS patients, and NIH has supported several research projects to address this issue. For example, researchers at the CC, in collaboration with extramural organizations, have sequenced nearly the entire genome of human, mouse, and rat Pneumocystis. Pneumocystis causes a life-threatening pneumonia in immunosuppressed hosts, including patients with HIV/AIDS, and has been responsible for thousands of deaths over the past 30 years. Analysis of the genomes has led to a better understanding of the unusual biology of Pneumocystis, and how it co-exists with its mammalian hosts.[1038] Furthermore, NICHD-supported

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[1033] HIV-1 and HIV-2 are the two main types of HIV virus. HIV-1 is the most widespread, and generally, when the type of HIV is not indicated, HIV-1 is being referred to.
[1034] https://grants.nih.gov/grants/guide/pa-files/PA-15-271.html.
[1035] Persaud D, et al. *N Engl J Med* 2013;369(19):1828-35. PMID: 24152233.
[1036] https://www.niaid.nih.gov/news-events/nih-trial-tests-very-early-anti-hiv-therapy-hiv-infected-newborns.
[1037] Coovadia A, et al. *JAMA* 2015;314(17): 1808-17. PMID 26529159.
[1038] Ma L, et al. *Nat Commun* 2016;7:10740. PMID 26899007.

researchers assessed immunity to common childhood infections in a follow-up study of individuals exposed to HIV in the womb—including children who developed HIV infection and those who did not. On average, children infected with HIV were much less likely to have protective levels of antibodies against measles, mumps, and rubella than did a group of children exposed to HIV in the womb but who remained uninfected. The results showed that it is possible that between one-third and one-half of individuals in the U.S. who were infected with HIV around the time of birth may not have sufficient immunity to ward off measles, mumps, and rubella—even though they may have been vaccinated against these diseases.[1039]

It has been reported that a number of factors, including the level of HIV-driven immune dysfunction, changes in saliva composition, presence of advanced caries, and periodontitis can influence persistent oral OIs. NIDCR-supported researchers reported that persistent oral OIs, due to HIV infection and ART, cause changes in the oral microbiome. They showed distinctive microbiome composition in three groups including HIV infected subjects before ART, HIV infected subjects after receiving ART, and non-HIV infected subjects. These findings demonstrate that HIV infection and subsequent ART cause importantsignificant changes in the oral microbiota and could offer a new therapeutic avenue to treat OIs by modifying the oral microbiome.[1040] A related study further highlighted the importance of the oral microbiome in regulating OIs. Oropharyngeal candidiasis, a fungal infection caused by a type of yeast called Candida, is the most common oral manifestation affecting millions of HIV/AIDS patients. NIDCR supported the first in vivo study that demonstrated that specific bacteria in the mouth could increase the virulence of Candida. The study also showed that the presence of Candida in the oral cavity and gastrointestinal tract of mice attracted other bacteria, like *Streptococcus oralis*, to colonize. In turn, the bacterial infection promoted the spread of the initial fungal infection to other organs.[1041]

HIV/AIDS patients are living longer lives and are facing aging-related diseases. In 2015, NIAID and NHLBI launched REPRIEVE/A5332, a Phase IV study to evaluate the effect of pitavastatin to prevent cardiovascular events such as heart attacks, strokes, and heart disease in HIV-infected individuals in the U.S., Canada, Thailand, and Brazil. This is the largest randomized clinical trial to date focused on HIV-related cardiovascular disease. Additional pilot studies and sub-studies will contribute to our understanding of biomarkers, chronic inflammation, and immune activation associated with comorbidities and HIV treatment.[1042] In 2015, NIAID-supported Strategic Timing of ART (START) investigators reported that starting ART early, without waiting for CD4+ cell counts to decline, not only prevents serious AIDS-related diseases, but also prevents non-AIDS-related diseases in HIV-infected people. Overall, the risk of developing serious AIDS events, developing serious non-AIDS events, or death was reduced by 57 percent among those who received early treatment, compared to those who started treatment after their CD4+ cell counts had declined below a certain threshold. Serious AIDS-related events (such as AIDS-related cancers) were reduced by 72 percent and serious non-AIDS events

[1039] Purswani MU, et al. *Clin Infect Dis* 2016;62(1):106-14. PMID 26385992.
[1040] Li Y, et al. *J Clin Microbiol* 2014;52(5):1400-11. PMID: 24523469.
[1041] Xu H, et al. *Cell Microbiol* 2014;16(2):214-31. PMID: 24079976.
[1042] https://www.niaid.nih.gov/news-events/nih-launches-largest-clinical-trial-focused-hiv-related-cardiovascular-disease.

(such as cardiovascular disease, end-stage renal disease, liver disease, non-AIDS defining cancers, or causes of death not attributable to AIDS) were reduced by 39 percent.[1043]

Malaria

Malaria continues to be a significant health risk worldwide. NIH conducts and supports research on risk factors, basic understanding of the mosquitoes carrying the parasites that cause malaria infection, treatment, and vaccination. NIH funding for malaria research was $169 million in FY 2014 and $163 million in FY 2015.[1044]

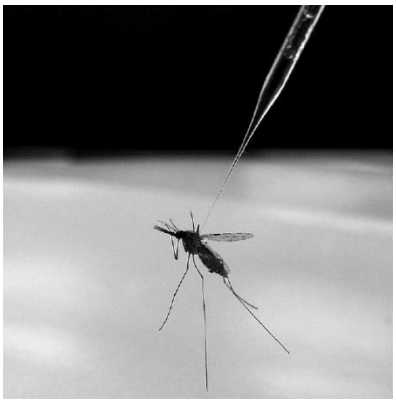

Figure 43. An *Anopheles gambiae* mosquito is injected with hemolymph for an NIH-funded malaria research study. Anopheles mosquitoes in nature are known for spreading the malaria-causing parasite Plasmodium. Credit: NIAID.

Female mosquitos from the genus *Anopheles* carry malaria vectors and spread the disease to humans. One approach for controlling the rate of malaria infection is the control of the mosquito population. NIAID Intramural investigators conducted a five-year study of sub-Saharan mosquito population densities to determine how these malaria vectors persist in arid areas, where the surface waters required for larval development are absent for several months a year. Using seasonal population information and modeling, researchers determined that, depending on the species, mosquitos can persist either by entering a dry season-induced dormant state (aestivation) or by long-distance migration (LDM) to exploit an arid environment such as the Sahel. Understanding mosquito vector dormancy and LDM is key to predicting shifts in the range of malaria due to global climate change, and to the elimination of malaria from Africa.[1045] Furthermore in FY 2014, NIAID-supported scientists determined that certain mosquito nerve cells, known as cpA neurons, cause mosquitoes to be attracted to humans by detecting exhaled carbon dioxide and odors emitted from human skin. Their findings may have implications for the control of mosquitoes and the diseases they transmit.[1046]

Some individuals exhibit resistance to severe malaria infections, and the mechanisms of such resistance are not fully understood. One hypothesis for malaria resistance is control of the mosquito populations.

[1043] INSIGHT START Study Group, et al. *N Engl J Med* 2015; 73(9):795-807. PMID 26192873.
[1044] https://report.nih.gov/categorical_spending.aspx.
[1045] Dao A, et al. *Nature* 2014;516(7531):387-90. PMID: 25470038.
[1046] Tauxe GM, et al. *Cell* 2013;155(6):1365-79. PMID: 24315103.

To test this hypothesis, NIAID Intramural investigators completed an intensive birth cohort study of 882 children in northeastern Tanzania who were followed for up to four years for malaria. The results indicated that naturally acquired resistance to severe malaria is not explained by improved control of parasite density.[1047] Variations in red blood cells can also protect African children from severe malaria infections. However, the genetic factors regulating this variation are poorly understood. NIAID Intramural researchers sought to characterize how five different variations in red blood cells are protective of malaria infection. Interestingly, they reported that a mutation of a gene on the X chromosome, a sex chromosomes present in two copies in girls and one copy in boys, was protective of malaria infection. Given the sex-linked nature of the gene, the mutation is protective in girls only. Meanwhile, HbC-trait, in which the body makes an abnormal hemoglobin called hemoglobin C, appeared to increase malaria risk in children. Scientists hope this study will lead to further research into the molecular mechanisms of the malaria-protective effects of red blood cell variants.[1048]

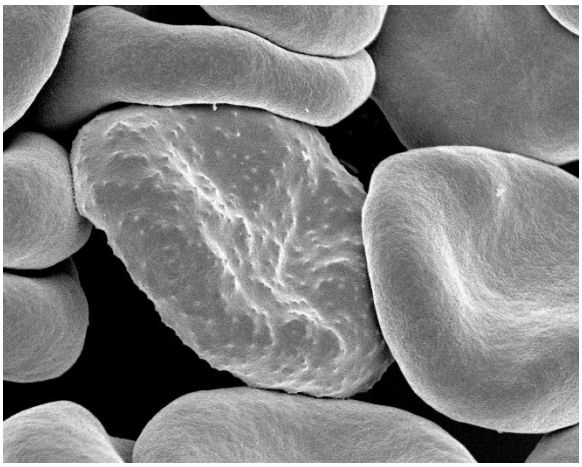

Figure 44. Electron micrograph of red blood cells infected with *Plasmodium falciparum*, the parasite that causes malaria in humans. Credit: Rick Fairhurst and Jordan Zuspann, NIAID.

Growing resistance to anti-malarial drugs has led to an urgent need to develop new treatments. To achieve this goal, NCATS researchers and collaborators released a large dataset of potential drug combinations for malaria. Using NCATS' state-of-the-art high-throughput combination drug-screening platform, NCATS's researchers tested 13,910 combinations of known and newly identified antimalarial drugs in three malaria parasite lines. The screening analyses done by the research team not only led to the identification of new combination therapies but also provided insights into the basic biology of malaria that the research community can build upon.[1049] Additionally, in FY 2014, NIAID-funded investigators identified the protein essential to all stages of the malaria parasite's life cycle. When tested in infected mice and nonhuman primates, a newly identified class of anti-malaria drug compounds, known as imidazopyrazines, inhibited the protein and stopped parasite development.[1050]Treating complications associated with malaria infection are also of interest. Cerebral malaria is a severe

[1047] Gonçalves BP, et al. *N Eng J Med* 2014;370(19):1799-808. PMID: 24806160.
[1048] Lopera-Mesa TM, et al. *Lancet Haematol* 2015;2(4):e140-9. PMID: 26687956.
[1049] https://ncats.nih.gov/pubs/features/matrix-malaria.
[1050] McNamara CW, et al. *Nature* 2013;504(7479)248-53. PMID: 24284631

neurological complication associated with malaria infection. Researchers supported through the NIAID International Centers of Excellence for Malaria Research found that increased intracranial pressure may be contributing to fatal outcomes among children with cerebral malaria. The findings suggest that interventions that decrease brain swelling may reduce mortality.[1051]

Developing an effective vaccine against malaria will result in decreased malaria infections and deaths associated with malaria. NIAID Intramural scientists and researchers at Rhode Island Hospital/Brown University have identified a malaria protein, PfSEA-1, that can elicit an antibody response to minimize multiplication of malaria parasites. A vaccine based on this protein, which may protect against severe malaria infection, was tested in mice and showed potential as a stand-alone or complementary vaccine to target different stages of malaria infection.[1052] Additionally, NIAID Intramural scientists have developed a malaria vaccine composed of two proteins essential for the invasion of red blood cells by the malaria-causing parasite *Plasmodium falciparum*. Vaccinated mice were protected from a highly virulent mouse strain of malaria.[1053] Both vaccines studies show promise in developing an effective vaccine to prevent malaria infection.

Tuberculosis

TB, a disease caused by the bacterium *Mycobacterium tuberculosis*, often affects the lungs of an infected individual. It was responsible for 1.8 million deaths in 2015.[1054] While antibiotics have historically been effective for treating TB, several antibiotic resistant strains have emerged, necessitating improved treatment options. Researchers supported by NIH are seeking to identify new treatments or determine which patients can be effectively treated by existing treatments. In FY 2014 and FY 2015, NIH devoted $279 million and $272 million, respectively, to TB research.[1055]

NIAID Intramural investigators have established proof-of-concept for host-directed TB therapy. This treatment involves manipulating the body's own immune response to *M. tuberculosis* rather than targeting the bacteria themselves, a concept called host-directed therapy. Investigators found that interleukin-1, a type of protein that regulates the body's immune response to infection, can help protect the body from TB infection. Their studies in cells and in mice and human patients infected with *M. tuberculosis* demonstrated that interleukin-1 induces a mediator, prostaglandin E2 (PGE2), that limits the production of type-I interferons, which are associated with increased TB disease severity.[1056]

Understanding whether a particular strain of *M. tuberculosis* will respond to traditional treatment will lead to better clinical outcomes. Several groups supported by NIAID have been developing approaches for screening patients with TB prior to treatment. Using a sensitive aptamer-based, proteomic technology, NIAID-supported researchers identified a set of five treatment response markers that

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[1051] Seydel KB, et al. *N Eng J Med* 2015;372(12)1126-37. PMID: 25785970
[1052] Raj DK, et al. *Science* 2014;344(6186):871-7. PMID: 24855263.
[1053] Srinivasan P, et al. *Proc Nat Acad Sci USA* 2014;111(28): 10311-6. PMID: 24958881.
[1054] http://www.who.int/mediacentre/factsheets/fs104/en/.
[1055] https://report.nih.gov/categorical_spending.aspx.
[1056] Mayer-Barber KD, et al. *Nature* 2014;511(7507):99-103. PMID 24990750.

identify patients who are responding well to two months of intensive phase treatment. In collaboration with the CDC, researchers conducted a pilot study and report that the set of markers can accurately predict a patient's eight-week culture status, are quantitative, and do not require culturing the pathogen.[1057] In another study, NIAID Intramural scientists and their colleagues examined changes on CT and positron emission tomography (PET)/CT images in a small group of patients with multidrug-resistant TB (MDR-TB) affecting the lungs. They found that changes in disease activity measured by these methods more accurately predicted patient outcomes than did traditional sputum cultures.[1058,1059]

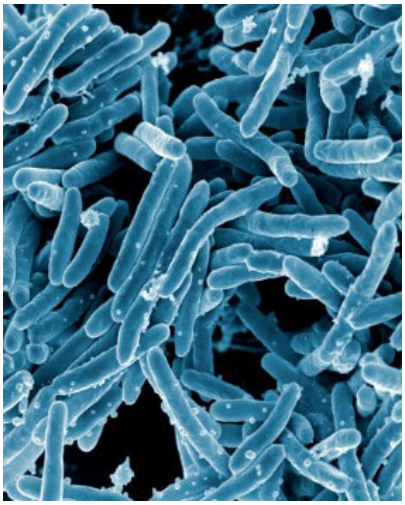

Figure 45. Scanning electron micrograph of *Mycobacterium tuberculosis* bacteria, which cause tuberculosis. Credit: NIAID.

Genomics also will provide a greater understanding of whether a patient with TB can be treated effectively with antibiotics. A NIAID-supported research team identified a set of genetic mutations that predict clinical drug resistance to six anti-TB drugs that are used to treat patients, including MDR-TB patients. These genetic mutations in *M. tuberculosis* have been found in patients from four countries, thereby representing a very diverse global population.[1060]In addition, a NIAID-supported study used genomic sequencing technology and computational tools for comparing genetic sequences to investigate the evolution of antibiotic resistance in bacteria that cause TB. The researchers studied samples collected over a 40-year period in South Africa and were able to determine when mutations conferring drug resistance occurred. This study provides valuable insight into the sequence of events that lead to drug resistance and informs strategies to prevent such resistance.[1061]

Viral Hepatitis

Infection with hepatitis viruses is the most common cause of acute and chronic liver disease in the U.S. and worldwide. At least five different hepatitis viruses (A, B, C, D, and E) can cause acute hepatitis, while

[1057] Nahid P, et al. *Tuberculosis* 2014;94(3):187-96. PMID: 24629635.
[1058] Coleman MT, et al. *Sci Transl Med* 2014;6(265):265ra167. PMID: 25473035.
[1059] Chen RY, et al. *Sci Transl Med* 2014;6(265):265ra166. PMID: 25473034.
[1060] Rodwell TC, et al. *J Clin Microbiol* 2014;52(3):781-9. PMID: 24353002.
[1061] Cohen KA, et al. *PLoS Med* 2015;12(9):e1001880. PMID: 26418737.

hepatitis B, C, and D viruses can also lead to a chronic infection. An effective vaccine against hepatitis B virus (HBV) has long been available and has resulted in dramatic reduction in new infections. For those already infected, an array of new treatment options have been developed, but these treatments do not lead to a permanent cure. In contrast, there are several new drugs and treatment regimens that can cure most hepatitis C virus (HCV) infections, but a vaccine against HCV is still lacking. NIH funding for viral hepatitis research was $251 million in FY 2014 and $262 million in FY 2015.[1062] NIDDK, together with NHLBI and NICHD, supported initiatives in 2015 to encourage small businesses to address viral hepatitis research opportunities.[1063,1064]

Hepatitis B Virus

While a vaccine for HBV has been available since 1980, treatments for those already infected do not result in a cure. Therefore, NIH continues to support the development of HBV treatments. NIDDK released an initiative in 2014 to continue support for projects within the Hepatitis B Research Network for up to five years. This network aims to advance understanding of disease processes and natural history of chronic HBV and to identify effective approaches to treatment with currently available therapies. [1065] Through public-private partnerships and collaboration with CDC, this multi-center network with sites throughout the U.S. and Canada, initiated multiple clinical trials and ancillary studies in FY 2014 and 2015 involving both adults and children with HBV. Additionally, network investigators target enrollment of special populations, including infected pregnant women, those with acute HBV infections, individuals co-infected with hepatitis D virus (HDV), and chronically infected individuals experiencing disease flares. An ancillary study to the network focuses on individuals co-infected with both HIV and HBV. NIAID supports contracts to conduct in vitro screening of candidate drugs for HBV infection. In FY 2014, 298 compounds were tested in primary assays for HBV antiviral activity. Four of these compounds underwent secondary screening. One such example of a compound tested is SB 44. This drug first went through NIAID in vitro screening and was found to be effective against HBV and HCV. SB 44 was tested in the NIAID-supported HBV transgenic mouse model to determine dose range, bioavailability and pharmacokinetics, tissue distribution, and toxicity. Results from these studies helped refine the drug, now called SB 9200, so that it could move forward in development.

Hepatitis C Virus

While HCV often can be cured, a vaccine to prevent infection does not yet exist. NIH supports vaccine development research. NIAID continues to support a Phase I/II trial to evaluate the safety, immunogenecity, and initial efficacy of a vaccine to prevent acute and chronic HCV infection. In a study supported by NIDDK, NIAID, NCI, and NIDA resulted in the development of a biologically relevant cell culture model of HCV. [1066] This research enhanced studies of HCV biology by enabling new cell culture

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[1062] https://report.nih.gov/categorical_spending.aspx.
[1063] https://grants.nih.gov/grants/guide/pa-files/PA-15-076.html.
[1064] https://grants.nih.gov/grants/guide/pa-files/PA-15-077.html.
[1065] http://www.hepbnet.org.
[1066] Saeed M, et al. *Nature* 2015;524(7566):471-5. PMID 26266980.

models of the wide variety of HCV genotypes found in infected patients and opened up new means of assessing vaccines against hepatitis C. In another study, scientists turned conventional wisdom—that low-level exposure to HCV protects against subsequent, full-strength encounters with the virus—on its head, finding instead that, in an animal model, such exposures may put individuals at risk for future infection by suppressing immune function. This finding is relevant to designing effective vaccination strategies against HCV and other microbes to which humans can be repeatedly exposed, such as those that cause malaria, TB, and HIV/AIDS.[1067]

In addition to supporting vaccine development, NIH supports research on improving HCV treatment. NIAID Intramural investigators conducted a small proof-of-concept study demonstrating cure from HCV infection in 98 percent of participants with only six weeks of therapy. Investigators added an HCV polymerase inhibitor, a chemical that inhibits replication of HCV RNA, to a combination of established direct-acting antivirals (sofosbuvir plus ledipasvir). This combination of drugs essentially led to a cure of HCV in 6 rather than 12 weeks.[1068] The same group demonstrated that a 12-week treatment of sofosbuvir and ledipasvir in previously untreated patients with HCV and HIV co-infection resulted in a 98 percent rate of sustained virologic response, a proxy for a cure, with no adverse effects.[1069] Researchers in NIDDK's IRP, in collaboration with NCATS, also screened over-the-counter drugs to select one that also has activity against HCV in cell and animal models. They found the drug with the greatest activity was chlorcyclizine, a commonly used antihistamine that is typically prescribed to treat symptoms of the common cold or hayfever allergy. Future research will explore ways to biochemically modify the drug to reduce levels in the brain and increase the activity against HCV, thus adding to its efficacy and reducing side effects.[1070]

Hepatitis D Virus

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 HDV. This first human trial shows the promise of lonafarnib as a potentially groundbreaking new type of therapy for chronic HDV. Future studies will explore long-term therapy, dose adjustment, and combination with drugs to increase the antiviral activity and reduce side effects of treatment.[1071]

Emerging Infectious Diseases and Biodefense (Including Seasonal and Pandemic Influenza)

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. Recognizing the potential for deliberate use of microorganisms as biological weapons, and the fact that previously

[1067] Park SH, et al. *Nat Med* 2013;19(12):1638-42. PMID: 24270546.
[1068] Kohli A, et al. *Lancet* 2015;385(9973): 1107-13. PMID: 25591505.
[1069] Osinusi A, et al. *JAMA* 2015;313(12):1232-9. PMID 25706232.
[1070] He S, et al. *Sci Transl Med* 2015;7(282):282ra49. PMID 25855495.
[1071] Koh C, et al. *Lancet Infect Dis* 2015;15(10):1167-74. PMID 26189433.

controlled microorganisms can re-emerge with new properties (such as drug resistance) or in new settings, NIAID has integrated its biodefense research into the Institute's larger emerging and re-emerging infectious disease portfolio.

Emerging and re-emerging diseases such as influenza, Ebola, and Middle East respiratory system coronavirus (MERS-CoV) are detrimental to health worldwide. The 2014-2015 influenza season resulted in nearly 1 million hospitalizations in the U.S.[1072] The 2014 Ebola outbreak in West Africa resulted in more than 11,000 deaths worldwide. There were an estimated 30,000 cases of Ebola during the outbreak, including four in the U.S.[1073] Since 2012, 27 countries have reported cases of MERS-CoV, which has led to 693 deaths.[1074] In addition to research on influenza, Ebola, and MERS, NIH also supported research on the following emerging infectious diseases or infectious agents:

- *Anthrax:* NIAID Intramural scientists were issued a U.S. patent for monoclonal antibodies that neutralize anthrax toxins. The causative agent of anthrax infection, *Bacillus anthracis*, is a Category A biodefense pathogen. The bacterium is highly stable in spore form, able to survive in harsh conditions for decades, and is very lethal to humans; because of this stability and lethality, *B. anthracis* is of great interest as a biological weapon. The patented monoclonal antibodies represent a promising and innovative approach to treating the toxicity in the case of a health emergency related to anthrax exposure.[1075]
- *Chikungunya:* Detected in the Caribbean in late 2013, chikungunya virus has infected hundreds of thousands of people in more than 20 countries in the Americas. It could become firmly established in the Western Hemisphere, posing a potential threat to the U.S. In FY 2015, NIAID, with the Pan American Health Organization and WHO, cohosted the workshop *Gaps and Opportunities in Chikungunya Research: Expert Consultation in Chikungunya Disease in the Americas*. Scientists, clinicians, epidemiologists, representatives from public health organizations and research funding organizations from around the world discussed chikungunya disease, epidemiology, and pathogenesis; opportunities to address the prevention, diagnosis, treatment, and control of chikungunya disease; identify gaps in knowledge, technologies, and research infrastructure; and assess the chikungunya epidemic risk throughout the Americas.[1076]
- *Dengue:* A tetravalent dengue vaccine developed by NIAID Intramural investigators elicited robust and balanced immune responses to all four dengue virus strains in healthy adults. Two randomized, placebo-controlled trials were performed to demonstrate the safety and immunogenicity of the live attenuated vaccine, which includes an enhanced dengue virus component, compared to an earlier trivalent vaccine version. A single subcutaneous dose of the dengue vaccine is safe and induces an antibody response to all four dengue strains at an unprecedented frequency among participants.[1077]

[1072] https://www.cdc.gov/flu/about/disease/2014-15.htm.
[1073] https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html.
[1074] http://www.who.int/emergencies/mers-cov/en/.
[1075] Patent number: US8961975 B2
[1076] https://respond.niaid.nih.gov/conferences/chikungunya/Pages/default.aspx.
[1077] Kirkpatrick BD, et al. *J Infect Dis* 2015;212(5):702-10. PMID: 25801652.

- *Foodborne Illness:* Approximately 48 million people each year affected by foodborne illnesses. NLM began a collaboration with CDC, FDA, the U.S. Department of Agriculture (USDA), and state and regional labs in 2014 to apply whole genome sequencing for surveillance and investigation of foodborne diseases. NLM is processing sequence reads for reported cases of common pathogens, such as *Listeria*, analyzing the data, and providing reports to the collaborators to more rapidly detect and identify the source of the outbreaks. The project has already quickly identified sources of food pathogens and helped resolve a number of disease outbreaks, thereby contributing significantly to public health. This project was a named a Secretary's Pick in the 2014 HHS Innovates contest. NLM also funded a study to include foodborne illnesses in the highly used HealthMap public health platform for predicting disease outbreaks, allowing for estimation of the extent of foodborne illness outbreaks. During the first year, investigators developed data mining and machine learning approaches for extracting, filtering, and processing data, and established partnerships with local and national public health organizations.[1078]
- *Lassa Virus (LASV):* An international team of researchers has developed the largest genomic dataset in the world on LASV. The new genomic catalog contains nearly 200 viral genomes collected from patient samples in Sierra Leone and Nigeria, as well as field samples from the major animal reservoir, or host, of LASV—the rodent *Mastomys natalensis*. The researchers show that LASV strains cluster into four major groups based on geographic location, with three in Nigeria and one in Sierra Leone, Guinea, and Liberia. Although Lassa fever was first described in modern-day Nigeria in 1969, the study also suggests that these four LASV strains originated from a common ancestral virus more than 1,000 years ago and spread across West Africa within the last several hundred years. The study offers new information about LASV mutations and its replication in infected individuals, which may help scientists understand how the virus causes infection and evades the immune response, and why clinical outcomes can differ so widely.[1079]
- *Parasitic Diseases:* Efforts to eliminate the parasitic diseases onchocerciasis and lymphatic filariasis in Central Africa through administration of the drug ivermectin have been suspended due to severe adverse drug reactions in individuals coinfected with the helminth *Loa loa*. A new mobile phone-based video microscope, CellScope Loa, automatically quantifies *L. loa* microfilarial parasites in whole blood samples and is the result of an innovative collaboration between NIAID IRP researchers and University of California, Berkeley, scientists. Use of this technology to exclude *L. loa*-infected patients from ivermectin-based treatment at the point of care in endemic regions would allow resumption and expansion of mass drug administration programs for onchocerciasis and lymphatic filariasis in Central Africa.[1080]
- **Pneumonic Plague:** In collaboration with FDA, NIAID supported the testing of licensed antibiotics for efficacy against pneumonic plague. These studies led to the first label indication for pneumonic plague based on efficacy data under the Animal Rule. In 2012, an FDA advisory committee reviewed data presented in support of ciprofloxacin and levofloxacin as treatments

[1078] Nsoesie EO, et al. *Prev Med* 2014;67:264-9. PMID: 25124281.
[1079] Andersen KG, et al. *Cell* 2015;162(4):738-50. PMID: 26276630.
[1080] D'Ambrosio MV, et al. *Sci Transl Med* 2015;7(286):286re4. PMID: 25947164.

for pneumonic plague. These antibiotics were subsequently approved by FDA in 2012 and 2015, respectively.[1081]

Influenza

A priority in emerging infectious diseases includes seasonal and pandemic influenza. Influenza remains a significant public health challenge, due in part to the limitations of current influenza vaccines and treatments. NIH devoted $262 and $280 million to influenza research in FY 2014 and FY 2015, respectively.[1082] Influenza research funded by NIH is largely focused on understanding the molecular basis of influenza infection, improving current vaccination efforts, and developing a universal vaccine.

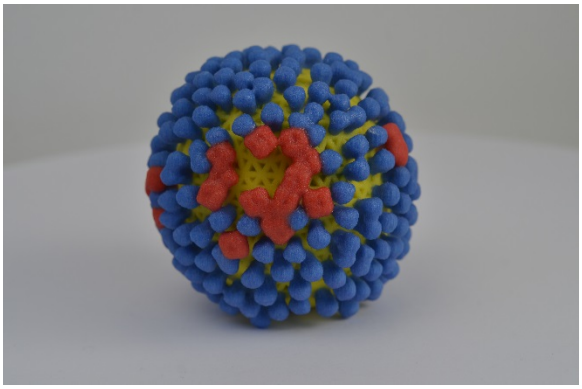

Figure 46. 3D print of influenza virus. The virus surface (yellow) is covered with proteins called hemagglutinin (blue) and neuraminidase (red) that enable the virus to enter and infect human cells. Credit: NIH 3D Print Exchange.

In FY 2014, NIAID funded five Centers of Excellence for Influenza Research and Surveillance (CEIRS)[1083] to advance understanding of influenza viruses and how they cause disease. In addition to basic research, investigators in the CEIRS program also conduct domestic and international influenza surveillance studies with an emphasis on rapid characterization of viruses that have the potential to cause pandemics.[1084] Additionally, NIAID Intramural investigators completed the first ever wild-type influenza A challenge study to gain critical information about the how the virus develops and persists, as well as specific information about how humans fight the infection. The data obtained from this study will provide a basis for more rapid, cost-effective clinical trials of new influenza drugs or determine the efficacy of candidate vaccines for both seasonal and pandemic influenza. A new challenge study of the H3N2 strain began December 7, 2015.[1085,1086]

[1081] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/019537Orig1s083,019847Orig1s055,019857Orig1s063,020780Orig1s041ltr.pdf.

[1082] https://report.nih.gov/categorical_spending.aspx.

[1083] http://www.niaidceirs.org/.

[1084] https://www.nih.gov/news-events/news-releases/nih-funds-influenza-research-surveillance-network.

[1085] Memoli MJ, et al. *Clin Infect Dis* 2015;60(5):693-702. PMID: 25416753.

[1086] https://clinicaltrials.gov/show/NCT01646138.

While vaccines against influenza have been effective in reducing the number of hospitalizations and deaths due to influenza infection, the effectiveness of such vaccines can vary widely from season to season.[1087,1088] Therefore, the NIAID influenza vaccine research program supports activities on innovative technology to improve production flexibility; new, more broadly protective vaccines; vaccines against newly emerging influenza viruses; and adjuvant development. VRC initiated trials to determine whether a DNA prime trivalent influenza vaccine would be more effective than the standard trivalent influenza vaccine.[1089,1090] Additionally, a Phase II trial conducted through the NIAID Vaccine and Treatment Evaluation Units found that a candidate H7N9 avian influenza vaccine was more effective when delivered with the MF59 adjuvant. Trial findings suggested that a single dose of adjuvant given with the first dose of vaccine may be sufficient to prompt a significant immune response.[1091]

Improving technology to increase vaccine compliance is also of interest to NIH. In 2014, nearly 100 healthy adults took part in a study on their ability and willingness to use a microneedle patch consists of 50 tiny needles, each about as tall as a credit card is thick, arranged at the center of a thin, flexible foam pad about the size of an adult fingertip. By far, participants preferred the microneedle patch over a traditional shot, whether self-administered or given by a trained medical professional. Besides being easy to use, the microneedle patch is also much smaller than typical flu vaccine supplies and does not need to be refrigerated, meaning it could potentially be sent through the mail or made available outside of traditional healthcare settings. In 2015, a clinical study of 100 participants to test the effectiveness of the influenza vaccine using this delivery method was started.[1092]

A top NIAID research priority is to develop a "universal" influenza vaccine that eliminates the need to constantly reformulate a seasonal vaccine in response to circulating influenza strains. One area of interest is bNAbs, a subset of antibodies that recognize regions of flu antigens conserved across multiple virus strains. In one study, researchers identified a novel mechanism by which these antibodies function to fight influenza infection, a discovery that can be used to inform vaccination strategies.[1093] Furthermore, with increasing understanding of the structure and immunological characteristics of the influenza surface protein hemagglutinin (HA), NIAID is moving closer to developing a universal flu vaccine. The "stem" portion of the HA molecule remains relatively constant among different influenza strains and is an attractive cross-protective immunologic target. VRC has developed an HA-ferritin nanoparticle vaccine that, in preclinical studies, elicited neutralizing antibodies (nAbs) to HA structures that are targets of universal vaccines.[1094] NIAID Intramural investigators also have shown that a vaccine developed using noninfectious virus-like particles offers significant protection against a variety of

[1087] https://www.cdc.gov/flu/about/disease/2014-15.htm.
[1088] https://www.cdc.gov/flu/about/qa/vaccineeffect.htm.
[1089] https://clinicaltrials.gov/ct2/show/NCT01498718.
[1090] https://clinicaltrials.gov/ct2/show/NCT01676402.
[1091] Mulligan MJ, et al. *JAMA* 2014;312(14):1409-19. PMID: 25291577.
[1092] Norman JJ, et al. *Vaccine* 2014;32(16):1856-62. PMID: 24530146.
[1093] DiLillo DJ, et al. *Nat Med* 2014;20(2): 143-51. PMID: 24412922.
[1094] Yassine HM, et al. *Nat Med* 2015;21(9):1065-70. PMID: 26301691.

influenza A viruses in mice, suggesting another practical strategy to develop a universal influenza vaccine.[1095]

Ebola Virus Disease

Ebola hemorrhagic fever is an acute viral disease that often leads to severe illness and death in humans and other primates. The infections typically affect multiple organs in the body and are often accompanied by hemorrhage (bleeding). Once the virus has been transmitted from an animal host to a human, it can then spread through person-to-person contact. NIH has been supporting Ebola research for many years, however, the levels of funding drastically increased in response to the deadly 2014 Ebola outbreak in West Africa. In FY 2014, NIH funding for Ebola was approximately $77 million. In FY 2015, the President requested and Congress appropriated $238 million to NIAID to prevent, prepare for, and respond to Ebola domestically and internationally.[1096] NIH supported research on sequencing the viral genome, vaccine development, and treatment, including treatment at the NIH CC. In addition, NIH grantees and collaborators played important roles in the Ebola response in affected countries in West Africa.

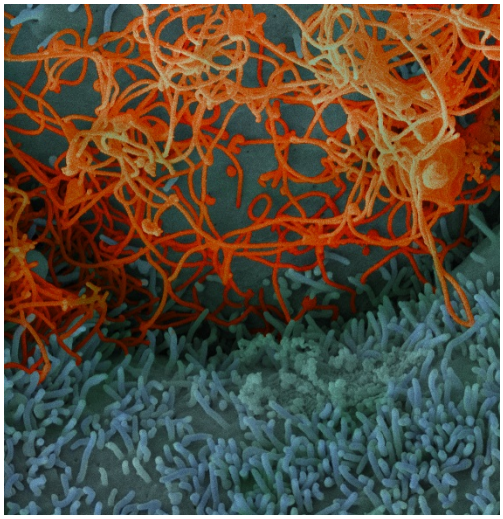

Figure 47. Ebola virus isolated from in November 2014 from patient blood samples obtained in Mali. Credit: NIAID.

The 2014 Ebola outbreak was the most deadly Ebola outbreak in history. Therefore, there was significant interest in the genomic sequence of the virus causing such dire consequences. Researchers hypothesized that the virus may be mutating twice as fast as previously observed in humans. If true, this would have serious implications for transmissibility and virulence, and could impede our ability to diagnose the disease. Using full-length genome sequencing of patients' samples from two independent introductions of the virus in Mali, NIAID Intramural scientists confirmed that Ebola virus did not undergo

[1095] Schwartzman LM, et al. *MBio* 2016;6(4):e01044. PMID: 26199334.
[1096] https://www.niaid.nih.gov/sites/default/files/FauciTestimony4-15-2015_v1.pdf.

accelerated mutation despite prolonged human-to-human transmission. The limited genetic change Ebola virus is undergoing in humans is unlikely to result in increased virulence or transmissibility.[1097]

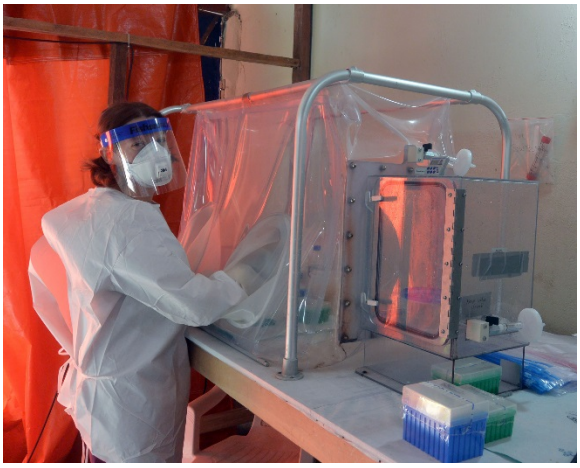

Figure 48. A NIAID researcher at a diagnostic laboratory in Monrovia during the 2014 Ebola outbreak uses a sealed glovebox to inactivate virus in patient blood samples prior to testing for Ebola. Credit: NIAID

Additionally, a Common Fund-supported New Innovator Awardee joined an international team of scientists using advanced genetic sequencing to identify a single point of infection from an animal reservoir to a human in the recent West Africa Ebola outbreak. This research revealed the dynamics of how the Ebola virus was transmitted from human to human, and traced how the genetic code of the virus changed over time to adapt to human hosts. Some of the mutations identified in their analyses alter the biological state of the virus and may have allowed it to continually and rapidly adapt to human immune defenses as the outbreak continued. The approach of collecting and analyzing data almost in real-time may help to establish a new paradigm for assessing and containing potentially catastrophic outbreaks.[1098]

Through the NIAID-funded Broad Institute Genomic Center for Infectious Diseases, NIAID supported the sequencing and comparative genomic analysis of Ebola virus isolated from patients infected during the 2014Ebola outbreak in West Africa. Researchers sequenced Ebola viral genomes of more than 660 human clinical samples. This work provided critical information about the genetic composition and variation of Ebola viruses circulating in West Africa. NIAID made these data rapidly available to the scientific community by submitting it to the National Center for Biotechnology public database GenBank. NIAID also supported the access and analysis of these data through its ViPR Bioinformatics Resource Center External Web Site Policy, which provides easy access to publicly available Ebola virus genomic sequences, clinical data associated with the samples, and data analysis tools.[1099,1100,1101]

[1097] Hoenen T, et al. *Science* 2015;348(6230):117-9. PMID: 25814067.
[1098] Gire SK, et al. *Science* 2014;345(6202):1369-72. PMID: 25214632.
[1099] https://www.viprbrc.org/brc/home.spg?decorator=filo_ebola.
[1100] https://directorsblog.nih.gov/2014/09/02/using-genomics-to-follow-the-path-of-ebola/.
[1101] Diehl WE, et al. *Epidemic Cell* 2016;167(4):1088–1098. PMID: 27814506.

The 2014 Ebola outbreak expedited some of the vaccine development efforts currently underway. In FY 2014 and 2015, NIAID accelerated the development, preclinical testing, and clinical evaluation of a novel immunization regimen using two Ebola vaccine candidates developed by two different pharmaceutical companies. NIAID also played an instrumental role in facilitating the collaboration between the companies. In addition, the NIAID preclinical services program supported the nonhuman primate studies required to demonstrate efficacy of the vaccine regimen. In December 2014, Phase I clinical trials began in the U.K. and U.S., followed by several sites in Africa.[1102] In collaboration with the University of Texas Medical Branch, NIAID Intramural scientists also developed and began testing an intranasal delivery Ebola vaccine candidate. An intranasal approach would be particularly valuable for pediatric populations as the nasal delivery may be easier to administer.[1103,1104]

After a safe and effective Phase I trial, VRC advanced an Ebola virus vaccine candidate, cAd3-EBOZ, in partnership with pharmaceutical company GlaxoSmithKline. The experimental Ebola vaccine is being tested for safety and immunogenicity in a Phase II/III clinical trial, which is enrolling volunteers in West Africa.[1105] An antiviral agent called BCX4430, developed by BioCryst Pharmaceuticals with support from NIAID, is an investigational small molecule drug with broad-spectrum antiviral activity, including against Ebola. Through its preclinical services contracts, NIAID supported the in vitro and in vivo screening of BCX4430, which protects animals against infection with Ebola and Marburg viruses. BioCryst and NIAID launched a Phase I clinical study in healthy volunteers in December 2014 to examine the product's safety and determine a treatment dosage.[1106] Further, the first in human testing of two vaccines against Ebola were conducted at the NIH CC.

In addition to vaccine clinical trials, NIH supported preclinical research to enhance the Ebola vaccine pipeline. Dual-purpose candidate vaccines to protect against both rabies and Ebola viruses were created by NIAID Intramural researchers in collaboration with investigators at Thomas Jefferson University (TJU). The vaccine candidates are being further developed through a partnership with German pharmaceutical company IDT Biologika, and have been licensed to Exxell BIO, which aims to advance the products through clinical testing and commercialization. NIAID and DoD are partnering with researchers at TJU to produce sufficient quantities of the candidate to begin clinical testing.[1107] Additionally, NIAID Intramural investigators tested a promising whole Ebola virus vaccine in monkeys. The vaccine, based on a defective form of the virus in which an essential viral gene (VP30) is knocked out, protected against a lethal challenge of Ebola. In limited immunological analyses, protection correlated with the production of antibodies against the Ebola envelope.[1108]

[1102] https://www.niaid.nih.gov/diseases-conditions/ebola-vaccines.
[1103] Meyer M, et al. *J Clin Invest* 2015;125(8):3241-55. PMID: 26168222.
[1104] https://clinicaltrials.gov/ct2/show/NCT02564575.
[1105] https://www.niaid.nih.gov/diseases-conditions/ebola-vaccines.
[1106] http://www.pharmaceutical-technology.com/news/newsniaid-grants-additional-funding-biocrysts-bcx4430-study-treat-ebola-disease-4357933.
[1107] Blaney JE, et al. *PLoS Pathog* 2013;9(5):e1003389. PMID: 23737747.
[1108] Marzi A, et al. *Science* 2015;348(6233): 439-42. PMID: 25814063.

At the onset of the 2014 outbreak, no licensed therapeutic was available for individuals infected with Ebola. Several groups conducted studies to develop novel approaches to treat Ebola patients. NIAID-supported researchers discovered that a cocktail of monoclonal antibodies, called ZMapp, rescued 100 percent of rhesus macaques when treatment was initiated up to five days post-challenge.[1109] A team of researchers from NCATS and the Icahn School of Medicine at Mount Sinai developed a miniaturized assay for high-throughput screening to find compounds that block the ability of Ebola virus-like particles (VLPs) to enter and infect cells. A screen using 2,816 compounds from the NCATS Pharmaceutical Collection identified 53 drugs with entry-blocking activity against Ebola VLPs. Further testing of these drugs may lead to a treatment for the Ebola.[1110] A NIAID-supported study showed that short interfering RNAs adapted to treat the Makona outbreak strain of Ebola-protected rhesus monkeys against lethal challenge.[1111] In a separate NIAID-supported study, researchers identified and characterized sections of two proteins that interact to regulate Ebola RNA synthesis, and demonstrated that a truncated version of one of the proteins was sufficient to inhibit Ebola RNA synthesis. This protein could serve as a potential target for antiviral therapy.[1112]

As mentioned in Chapter 1, the NIH CC played a key role in NIH's Ebola response, providing care to citizens who were exposed to or infected with Ebola following treatment of infected patients.[1113] Patient care took place in the CC Special Clinical Studies Unit, which is specifically designed to provide high-level isolation capabilities and is staffed by infectious disease and critical care specialists. The CC also supports the work of NIAID with the launch of the world's first human clinical trials of two promising Ebola vaccines.[1114] NIAID IRP scientists also responded to the Ebola virus outbreak by establishing and staffing laboratory sites in Monrovia, Liberia, in coordination with CDC and DoD to identify the presence of Ebola virus in clinical samples. These real-time data were critical to patient care and monitoring of the epidemic.

Furthermore, the NIEHS Working Training Program participated in the Ebola response by providing domestic Ebola preparedness training, administering supplemental funding to existing grantees for an Ebola Training Initiative, and developing several resources for grantees and others.[1115] Finally, NLM developed a number of resources to provide information on Ebola and organized and disseminated large volumes of information produced by the many groups responding to the outbreak. NLM created an online *Disaster Topic Page* was created to organize resources for healthcare and public health professionals and emergency management personnel. It was routinely updated, often on a daily basis, during the height of the outbreak. Likewise, a web page for the general public was developed for MedlinePlus. NLM and a number of publishers activated the Emergency Access Initiative (EAI) to ensure

[1109] Qiu X, et al. *Nature* 2014;514(7520):47-53. PMID: 25171469.
[1110] Kouznetsova J, et al. *Emerg Microbes Infect* 2014;3(12): e84. PMID: 26038505.
[1111] Thi EP, et al. *Nature* 2015;521(7552):362-5. PMID: 25901685.
[1112] Stuhlmiller TJ, et al. *Cell Rep* 2015;11(3): 390-404. PMID: 25865888.
[1113] Uyeki TM, et al. *N Engl J Med* 2016;374(7): 636-46. PMID: 26886522.
[1114] https://clinicalcenter.nih.gov/ebola1.html.
[1115] https://tools.niehs.nih.gov/wetp/index.cfm?id=2542.

that healthcare providers had access to critical information including online books, journals, and databases; EAI remained active through December 2014.

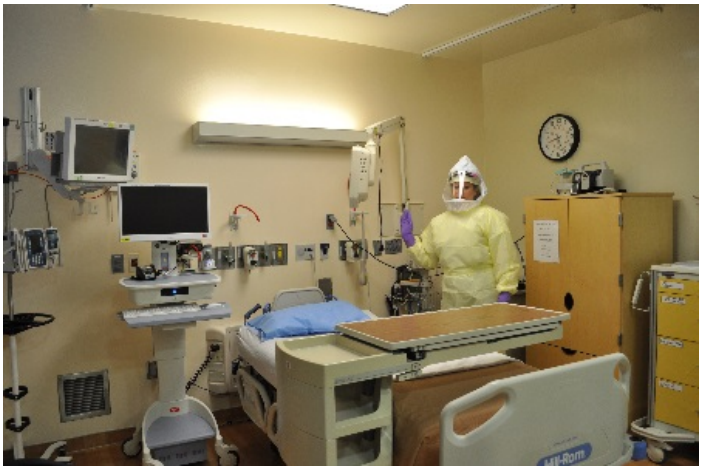

Figure 49. Special Clinical Studies Unit nurse Megan Schlosser stands in one of the unit's patient care rooms in the NIH Clinical Center. The SCSU was used to isolate and treat Ebola patients in 2015. Credit: NIH.

Middle East Respiratory Syndrome Coronavirus

Since the MERS-CoV outbreak in 2012, there have been nearly 2,000 confirmed cases and nearly 700 deaths from this infection.[1116] There are no known countermeasures to MERS-CoV, so NIAID-supported researchers have developed tools to understand MERS-CoV pathogenesis. In general, small animals are not permissive to MERS-CoV infection, so novel strategies are needed to make the animal susceptible to infection with the virus. NIAID-supported investigators described the generation of a transgenic mouse model that expresses the human receptor for MERS-CoV, allowing the animal to be infected with the virus. High virus titers were recovered from the lungs and brains of the transgenic mice, while viral RNA was detected in the heart, spleen, and intestines. In addition, the transgenic mice developed a progressive pneumonia with extensive inflammatory infiltration. These mice could be used to study MERS-CoV pathogenesis and develop medical countermeasures.[1117]

NIAID has also supported efforts to develop vaccines to prevent MERS-CoV infection. NIAID Intramural and VRC investigators developed two prospective MERS-CoV vaccines that have shown promise in nonhuman primates. In both instances, the vaccines induced protective immunity in the animals.[1118,1119] Furthermore, the NIH VRC developed candidate vaccines, including DNA or other gene-based vaccine approaches, purified protein subunit vaccines, and multivalent nanoparticles.[1119] The DNA vaccine development approach for MERS-CoV was informed by results from a by a severe acute respiratory

[1116] http://www.who.int/emergencies/mers-cov/en/.
[1117] Agarwal AS, et al. *J. Virol* 2015;89(7): 3659-70. PMID: 25589660.
[1118] Muthumani K, et al. *Sci Transl Med* 2015;7(301): 301ra132. PMID: 26290414.
[1119] Wang L, et al. *Nat Commun* 2015;6:7712. PMID: 26218507.

syndrome (SARS)–CoV vaccine candidate, developed by VRC several years ago, that was safe and produced immune responses in a Phase 1 human trial.[1120]

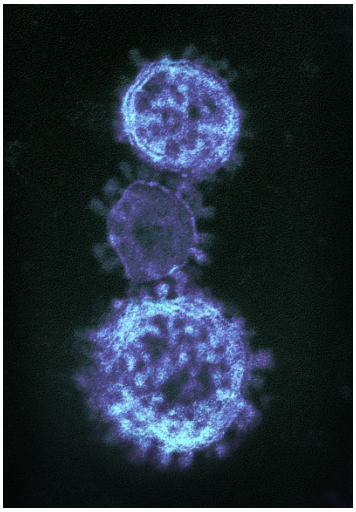

Figure 50. Transmission electron micrograph showing particles of the Middle East respiratory syndrome coronavirus (MERS-CoV). Credit: NIAID.

In addition to developing vaccines to prevent MERS-CoV infection, NIAID supported research to develop treatments for people who are already infected. Investigators isolated B cells from a patient infected with MERS-CoV and screened them for MERS-CoV nAbs. The team identified LCA60, which targets the MERS-CoV spike protein and efficiently neutralizes the virus. The antibody was also effective prophylactically and therapeutically in an animal model of MERS-CoV infection. The team demonstrated that a human antibody with therapeutic potential against MERS-CoV can be quickly isolated from B cells of an infected patient.[1121] In another study, NIH-supported researchers screened a set of 290 compounds already approved by FDA, or far advanced in clinical development for other indications, to determine whether any might also show potential for working against MERS-CoV. From the group of 290 compounds, the scientists identified 27 that, in test-tube experiments, showed activity against both MERS-CoV and the related SARS coronavirus. The active compounds belong to 13 different classes of pharmaceuticals and include drugs that inhibit the viruses' ability to enter and infect cells. Some of the active compounds are now being tested in mice experimentally infected with MERS-CoV.[1122]

Antimicrobial Resistance

Many infectious diseases are increasingly difficult to treat as pathogens develop resistance to antimicrobial drugs.[1123] For example, in recent years there have been dramatic increases in antiretroviral-resistant HIV, chloroquine- and artemisinin-resistant malaria, the emergence of multidrug-

[1120] Martin J, et al. *Vaccine* 2008;26(50):6338-43. PMID: 18824060.
[1121] Corti D, et al. *Proc Natl Acad Sci USA* 2015;112(33):10473-8. PMID: 26216974.
[1122] https://www.niaid.nih.gov/news-events/screen-existing-drugs-finds-compounds-active-against-mers-coronavirus.
[1123] https://www.niaid.nih.gov/research/antimicrobial-resistance.

resistant TB and extensively drug-resistant TB, carbapenem-resistant Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

NIH continues to support research into understanding the basis of resistant microbes, diagnosing resistant strains, and developing new treatments. In FY 2014, NIAID issued its *Antibacterial Research Program: Current Status and Future Directions* report, describing the Institute's basic, translational, and clinical research in AMR and outlining a combination of innovative approaches to pursue, based on the latest scientific advances.[1124]

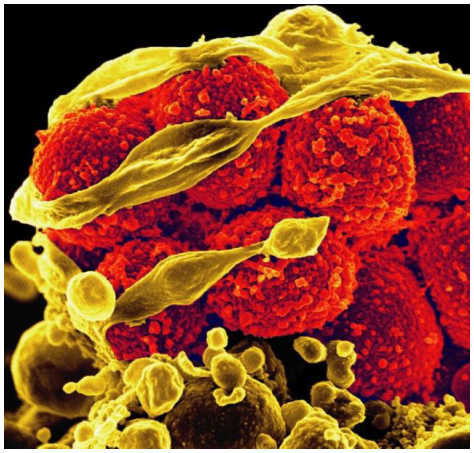

Figure 51. Scanning electron micrograph of methicillin-resistant *Staphylococcus aureus* bacteria (yellow, round items) killing and escaping from a human white cell. Credit: NIAID.

Understanding how a microbe becomes resistant to commonly used drugs can help researchers develop new drugs to circumvent that resistance. Several NIAID-funded projects uncovered mechanisms microbes use to render themselves resistant to treatment. NIAID Intramural investigators have identified key factors in resistance to artemisinin, a first-line treatment for malaria. The emergence and rapid spread of artemisinin-resistant *Pf*, the parasite that causes malaria, in Southeast Asia significantly threatens malaria management efforts. Researchers also showed that artemisinin-resistant *Pf* can replicate in a wide range of mosquito species, including mosquito species from Africa, meaning that Africa is at major risk for arteminisin-resistance spread, representing a major global health threat.[1125] Another group identified one of the molecular mechanisms that *Neisseria gonorrhoeae* uses to resist antibiotics and suggested that targeting this mechanism may allow healthcare providers to use classes of antibiotics that are currently not recommended for gonorrhea treatment.[1126]

Phylogenetic analyses have also been informative in understanding how microbes become resistant to antimicrobial agents. NIAID Intramural scientists have tracked the evolution of an antibiotic-resistant strain of the bacterium *Klebsiella pneumoniae*, a major cause of hospital deaths. Phylogenetic analysis of 85 clinical isolates revealed that *K. pneumoniae* multi-locus sequence type 258 organisms arose from at least two distinct lineages, with key differences in the bacterium's outer coat, the primary region that

[1124] https://www.niaid.nih.gov/sites/default/files/arstrategicplan2014.pdf.
[1125] Straimer J, et al. *Science* 2015; 347(6220):428-31. PMID: 25502314.
[1126] Golparian D, et al. *Antimicrob Agents Chemother* 2014;58(6): 3556-9. PMID: 24733458.

interacts with the human immune system.[1127] Another NIAID-supported study used genomic sequencing technology and computational tools for comparing genetic sequences to investigate the evolution of antibiotic resistance in bacteria that cause TB. The researchers studied samples collected over a 40-year period in South Africa and were able to determine when mutations conferring drug resistance occurred, providing valuable insight into the sequence of events that lead to development of drug resistance and informing strategies to prevent such resistance.[1128]

Determining whether a bacterial strain will respond to standard treatment will expedite the patient's treatment. NIAID supports a large research program focused on developing diagnostics to combat antibiotic resistance, including awarding more than $11 million in 2015 to support nine research projects focused on enhanced diagnostics to rapidly detect antimicrobial-resistant bacteria. These awards were made to three companies and six academic organizations that are developing diagnostics to enable rapid, sensitive, specific, culture-independent detection of high-priority antimicrobial-resistant bacteria.[1129] However, screening exclusively for highly resistant strains may not be beneficial. NICHD-supported researchers analyzed hospital records of newborns who had S. *aureus* infections in 348 neonatal intensive care units in 34 states to determine the predominant source of the infection: MRSA or methicillin-susceptible *S. aureus* (MSSA). Among 887,910 infants, MSSA infections made up slightly more than 72 percent of the total, while MRSA infections comprised nearly 28 percent. Overall, the infections were most common in very low birth weight infants, the smallest, most fragile class of preterm infants. For cases in which death records were available, 9.6 percent of infants with MSSA and 11.6 percent of infants with MRSA died before leaving the hospital. Based on these findings, researchers suggest that newborn care facilities consider expanding their infection screening programs to include MSSA as well as MRSA, since MSSA appears to pose an equally serious threat.[1130]

Finally, NIH supports research in developing new drugs or repurposing existing drugs to treat AMR. NIAID and Common Fund–supported researchers used an innovative method to screen uncultured bacteria from soil and identified a novel antibiotic, teixobactin. The drug inhibits bacterial cell-wall synthesis by binding to a highly conserved lipid motif and shows activity against drug-resistant microbes in a mouse model of infection. The researchers suggest that teixobactin's properties may help identify a path toward antibiotics that are likely to avoid development of resistance.[1131] NIAID and CDC scientists found that two new antibiotic regimens using existing drugs—injectable gentamicin in combination with oral azithromycin and oral gemifloxacin in combination with oral azithromycin—successfully treated gonorrhea infections.[1132] NIAID-supported researchers also found that two common antibiotic treatments work equally well to treat community-acquired MRSA.[1133]

[1127] Deleo FR, et al. *Proc Natl Acad Sci USA* 2014;111(13): 4988-93. PMID: 24639510.
[1128] Cohen KA, et al. *PLoS Med* 2015; 12(9): e1001880. PMID: 26418737.
[1129] http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-14-019.html.
[1130] Ericson JE, et al. *JAMA Pediatr* 2015; 169(12):1105-11. PMID: 26502073.
[1131] Ling LL, et al. *Nature* 2015; 517(7535):455-9. PMID: 25561178.
[1132] Kirkcaldy RD, et al. *Clin Infect Dis* 2014; 59(8): 1083-91. PMID: 25031289.
[1133] Miller LG, et al. *N Engl J Med* 2015;372(12):1093-103. PMID: 25785967.

A number of protocols to test therapeutics for resistant pathogens of concern are being conducted in NIAID-supported clinical trials networks, including studies evaluating new ways to treat gonorrhea, such as a Phase II trial of an investigational oral antibiotic and a Phase I trial assessing the pharmacokinetics of an oral next-generation macrolide. NIAID is also supporting a Phase I trial to evaluate safety and tolerability of CRS3123 as a potential treatment for *C. difficile,*[1134,1135] as well as a Phase I trial for nasal decolonization of *S. aureus* with a novel topical agent.[1136]

NIAID continues to support a number of diagnostics to combat antibiotic resistance, including multiplex platforms such as the FilmArray Blood Culture Identification Panel by BioFire Diagnostics LLC, an affiliate of Biomérieux. Through small business grants and partnerships, NIAID supported the development of this polymerase chain reaction (PCR)–based system, which has been cleared by FDA, to simultaneously detect several pathogens in patient samples in approximately one hour. This panel tests for 24 Gram-positive bacteria, Gram-negative bacteria, and yeast microbes that cause bloodstream infections.[1137]

As part of the March 2014 presidential initiative to combat antibiotic-resistant bacteria, the National Center for Biotechnology Information (NCBI) continues to collaborate with FDA, CDC, USDA, and other groups to maintain a database of whole genome sequencing data for antibiotic-resistant bacteria, along with tools to facilitate analyses of such data.[1138] The database provides an important resource for surveillance of and research into the mechanisms underlying the emergence of antibacterial resistance. Since this website became operational, it has received hundreds of antibiograms, both clinical and agricultural, from academic and government collaborators. NLM has also built a database of more than 3,000 resistance proteins that confer resistance to 33 drug classes.

Biodefense and Emerging Infectious Disease Infrastructure

NIH has invested substantially in the intellectual and physical infrastructure needed to build the nation's capacity for research on biodefense and emerging infectious diseases. This infrastructure is critical to the development of medical countermeasures and has increased the nation's ability to respond to new and re-emerging infectious diseases. Examples of projects supported by NIH to develop biodefense and infectious disease infrastructure are described below.

NIDCR supports an initiative to stimulate innovative research that would increase understanding of the role that uncultivable bacterial species play in health and disease. The effective integration of current technologies and the development of new tools and innovative methods were especially encouraged. Due to the wide spectrum of possible experimental approaches and the multidisciplinary tools that would be required to study this unique microbial population, the initiative encourages team science that

[1134] https://clinicaltrials.gov/ct2/show/NCT01551004.
[1135] https://clinicaltrials.gov/ct2/show/NCT02106338.
[1136] https://clinicaltrials.gov/ct2/show/NCT02282605.
[1137] Buss SN, et al. *J Clin Microbiology* 2015;53(3):915-25. PMID: 25588652.
[1138] http://www.ncbi.nlm.nih.gov/bioproject/313047.

would leverage innovation, broad expertise, and multiple technological platforms to answer hypothesis-driven questions regarding these bacteria. Two projects were funded through this initiative.[1139]

The Research and Policy in Infectious Disease Dynamics (RAPIDD) program—co-funded by FIC and the Department of Homeland Security—brings together senior infectious disease modelers and postdoctoral fellows to develop infectious disease modeling approaches that can help the U.S. plan for and respond to potential infectious disease threats. RAPIDD models have contributed to a greater understanding of how avian influenza, as well as hand, foot, and mouth disease, can develop into outbreaks.[1140]

A public–private partnership spearheaded by the Bill & Melinda Gates Foundation brings drug companies together to share their compound libraries with NIAID Intramural scientists performing collaborative TB drug discovery research. Small molecule hits from a high-throughput screen are evaluated and undergo limited optimization to identify promising lead compounds that are quickly tested in a predictive animal model for further evaluation in humans, cutting this process from five years to less than six months; 3,200 hit compounds across 150 distinct chemical series have been identified. This process benefits from major FY 2014 advances in imaging techniques that predict treatment outcomes for TB patients two months into treatment more accurately than traditional sputum cultures do at 30 months.[1141]

The Clinical Genomics Program, which facilitates the application of advanced genomic technologies to multiple groups in NIAID, NHGRI, and the NIH CC, provides infrastructure for scientific interaction, data analyses, and genotype/phenotype sharing. The program also interfaces between NIAID and the new CC Genomics Opportunity program and has shown early success in launching two new clinical treatment trials based on gene identification.[1142]

The Platform for Modeling the Global Impact of Climate Change on Infectious Disease models global relationships between climate and disease risk and uses these models to project climate change's future effects on infectious disease risk. The results will also inform ongoing surveillance and impact assessments by international organizations, such as WHO and the Red Cross.[1143,1144]

The NIAID Division of Microbiology's Preclinical Services (PCS) Program, provides support through a variety of groups, including the Microbiology and Infectious Diseases Biological Resource Repository, Preclinical Services for Biopharmaceutical Product Development, Preclinical Models of Infectious Diseases, the In Vitro Assessments for Antimicrobial Activity program, Evaluation and Testing Services for Vaccines and Other Biologics for Infectious Diseases, Manufacture and Characterization Services for

[1139] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-14-003.html.
[1140] https://www.fic.nih.gov/about/staff/pages/epidemiology-population.aspx#rapidd.
[1141] https://www.niaid.nih.gov/news-events/imaging-techniques-reliably-predict-treatment-outcomes-tb-patients.
[1142] https://www.niaid.nih.gov/research/clinical-genomics-program.
[1143] Bogoch II, et al. *Lancet* 2015;365(9962):29-35. PMID: 25458732.
[1144] Majumder MS, et al. *JAMA Pediatr 2015;*169(5):494-5. PMID: 25774618.

Vaccines and Other Biologics for Infectious Diseases, and Preclinical Services for the Development of Interventional Agents for Infectious Diseases.[1145]

Public Health Emergency Preparedness

Public health emergencies arise when unexpected incidents, natural or manmade, have the potential to greatly influence human health, 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 ICs and grantees conduct research on disaster preparedness, response, and recovery issues. These efforts have contributed to a deeper understanding of disaster risks and recovery and can provide critical information when disasters strike. NIH supports research to address public health issues arising from natural and manmade disasters; biological, chemical, and radiological threats; and epidemics. NIH supports programs to help respond to public health emergencies in general and to specific types of incidents. NIH's efforts to respond to infectious disease crises, such as the Ebola outbreak in 2014, are highlighted in the infectious diseases and biodefense section of Chapter 3.

Emergency Preparedness Across NIH

In response to recent disasters and the research conducted in their wake, NIH initiated its Disaster Research Response (DR2) Program.[1146] This pilot program, developed by NIEHS and NLM, aims to create a disaster research system of coordinated environmental health disaster research, data collection tools, and a network of trained research responders. As part of the DR2 program, NIEHS designed the Rapid Acquisition of Pre- and Post-Incident Disaster Data (RAPIDD) study protocol.[1147] The primary objective of the RAPIDD study is to create a research registry of disaster response workers who are added to the registry before or immediately after deployment to a disaster area.[1148] The RAPIDD protocol has a flexible and scalable approach to fit varying conditions on the ground. Since some elements of a disaster cannot be specified in advance, RAPIDD has built in a customizable set of materials that can be readily reviewed and approved at the time of a disaster. To help researchers in making a timely selection of

[1145] https://www.niaid.nih.gov/research/microbiology-and-infectious-diseases-resources.
[1146] https://dr2.nlm.nih.gov/about.
[1147] https://disasterlit.nlm.nih.gov/resources/content/public/files/RAPIDD%20Protocol_v8.0_2015-07-16_508_CLEAN.pdf.
[1148] https://dr2.nlm.nih.gov/protocols.

data collection tools for medical and public health research, the DR2 Program has also compiled the Disaster Research Response Data Collection Tools database.[1149]

Figure 52. The NIH Disaster Research Response Program is working to create relevant environmental health data tools and a network of trained research responders. Credit: TFoxFoto/Shutterstock.com.

NLM develops and provides access to health information resources and technology for disaster and emergency preparedness, response, and recovery. The program, Disaster Lit,[1150] focuses on maintaining access to health information at all phases of disaster response, developing innovative products and services for emergency personnel, and conducting research to support disaster health information management. NLM's research and development in this area has led to development of tools and mobile health applications that enable remote collaboration, education, training, and access to NLM information resources and disaster aids anytime, anywhere, and from a variety of devices. For example, NLM's PEOPLE LOCATOR is a Web system that enables family, friends, and neighbors to locate or report missing people during a disaster event.[1151] The system utilizes a database containing data from the IT systems of local hospitals; additional input is accepted from triage-area cell phones and social networks. After the South Asian earthquake in December 2015, a Pakistani man's life was saved because NLM experts used the system, part of NLM's Lost Person Finder Project.[1152]

In addition to developing programs to aid public health crises in general, NIH responds to specific types of incidents. For example, in 2014 NLM responded quickly to a water safety incident in West Virginia by compiling technical information for decision making.[1153] Residents in the Elk River area reported a strong odor in their drinking water; the source of the odor was a leak in a storage tank that contained the chemical 4-methylcyclohexanemethanol (MCHM), which is used to wash coal and remove impurities that contribute to pollution when coal burns. There was little knowledge about the chemical's properties that could help determine the risks of exposure or how to clean up the spill. In collaboration with other government agencies and the Hazardous Substance Data Bank (HSDB) scientific review panel,

[1149] https://dr2.nlm.nih.gov/tools-resources.
[1150] https://disasterinfo.nlm.nih.gov/disaster-lit.
[1151] https://ceb.nlm.nih.gov/proj/lpf.php.
[1152] https://infocus.nlm.nih.gov/2015/12/18/how-nlm-technology-and-alertness-saved-a-life-in-south-asian-earthquake/.
[1153] https://infocus.nlm.nih.gov/2016/03/09/rapid-response-west-virginia-elk-river-2014-spill/.

NLM staff investigated the data available on the chemical in six days. A public record for MCHM in the HSDB was developed, and CDC posted the record on their 2014 West Virginia Chemical Release Emergency Preparedness & Response page. Later that month, the manufacturer that owned the tank reported that another substance, propylene glycol phenyl ether (PPH), was present in the tank and had also been released. Limited data on PPH was available before the incident; NLM developed another HSDB record on the chemical. NLM has periodically updated these HSDB records to share the ongoing research and findings from the National Toxicology Program related to this incident.

Figure 53. 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.

Chemical and Radiological/Nuclear Countermeasures

NIH supports research to test treatments for chemical and radiological/nuclear exposures. Countermeasures Against Chemical Threats (CounterACT) is a trans-NIH effort to develop medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disasters.[1154] The program completed early development of tissue plasminogen activator (tPA), a drug used to treat stroke, as treatment for sulfur mustard injury to the lungs.[1155] The HHS Biomedical Advanced Research and Development Authority (BARDA) program has awarded a contract for further development and FDA approval of this new application for tPA. A Phase III trial of midazolam for emergency seizures was successfully completed, and FDA approval of the use of this drug for seizures from nerve agents is likely in 2016. Antidotes for cyanide, sulfur mustard, nerve agents, and other chemical threats are also under development.

NIAID manages the NIH-sponsored Radiation and Nuclear Countermeasures Program (RNCP) that focuses on medical countermeasure (MCM) development, from early stage research to licensure, as well as on development of biodosimetry devices to assist in triage in mass-casualty radiation/nuclear incidents. Other areas of emphasis include elucidating mechanisms of radiation-induced injuries, developing animal models consistent with FDA Animal Rule licensure requirements for radiation indications, and identifying biomarkers of injury. Since the program's inception in 2005, more than 550

[1154] https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/CounterACT.
[1155] Veress LA, et al. *Am J Respir Cell Mol Biol* 2013; 48(4): 439-47. PMID: 23258228.

MCMs and biodosimetry approaches have been studied. Notably, in March and November 2015, FDA approved the use of Neupogen (filgrastim) and Neulasta (pegfilgrastim), to treat adults and children, respectively, who are acutely exposed to myelosuppressive doses of radiation that cause the hematopoietic syndrome of acute radiation syndrome. These FDA approvals were based on animal models and data from animal efficacy studies wholly supported by RNCP.

Rare and Undiagnosed Diseases

Today, more than 6,000 rare disorders affect a total of nearly 25 million Americans. A rare disease is defined as one that affects fewer than 200,000 people and may involve chronic illness, disability, and premature death.[1156] Rare diseases are often devastating and costly for patients, their families, and the nation as a whole, due to the severity of these conditions and because diagnosis can be difficult and often possible only long after symptoms have appeared. Treatment is often unavailable even after a disease is diagnosed, since it is difficult to recover the costs of developing treatments for small, geographically dispersed populations.[1157] Currently, there are treatments for only a few hundred diagnosed rare diseases.

Finding an underlying diagnosis for many conditions can be a long and frustrating experience.[1158] Individuals with rare conditions can go for extended periods without a diagnosis. These types of rare disorders are referred to as undiagnosed diseases.[1159] 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.

Summary of NIH Activities

NIH funding for rare diseases was $3,639 million in 2014 and $3,679 million in 2015. Because rare and undiagnosed diseases can impact any organ system, funded research and activities are conducted throughout NIH.[1160]

The Undiagnosed Diseases Network

One of the clinical research initiatives of the NIH that is designed to tackle undiagnosed diseases head on is the Common Fund's Undiagnosed Diseases Network (UDN).[1161] Building on the successes of the NIH Undiagnosed Diseases Program,[1162] which helps provide diagnosis and treatment for patients with

[1156] https://www.ncbi.nlm.nih.gov/medgen/146261#Definition.
[1157] https://report.nih.gov/biennialreport10-11/chapter4/NIH_RDCRN.html.
[1158] https://rarediseases.info.nih.gov/guides/pages/24/tips-for-the-undiagnosed.
[1159] https://www.nih.gov/news-events/undiagnosed-diseases-network-launches-online-application-portal.
[1160] https://report.nih.gov/categorical_spending.aspx.
[1161] https://commonfund.nih.gov/Diseases.
[1162] https://www.genome.gov/27544402/the-undiagnosed-diseases-program/.

unknown disorders, NIH extended the program into a network of seven clinical sites in 2014. These clinical sites, together with a UDN Coordinating Center and other Core Laboratories, comprise UDN and will serve to assess whether this type of cross-disciplinary approach to disease diagnosis could be implemented in academic medical centers around the U.S.[1163]

In 2015, UDN launched an online application portal called the UDN Gateway[1164] to advance the network's mission: to diagnose patients who suffer from conditions that even skilled physicians have been unable to diagnose despite extensive clinical investigation. The UDN Gateway will provide patients and their families access to the nation's leading diagnostic teams and sophisticated diagnostic tools. UDN will provide state-of-the-art genetic sequencing and clinical evaluation for patients whose conditions have thus far eluded diagnosis despite extensive testing. Discoveries made through this program may lead to treatments for individual patients who participate and may also lead to new medical insights into more common diseases and conditions.[1165]

The Rare Diseases Clinical Research Network

The Rare Disease Clinical Research Network[1166] (RDCRN) was established by the NIH ORDR in 2003 and now is overseen by NCATS (see Chapter 4 for a full update on this Center of Excellence). Since its launch, nearly 40,000 patients have been enrolled in network clinical studies. As of October 2014, the network consisted of about 2,600 researchers, including scientific program staff from NCATS and collaborating NIH components, academic investigators, and members of 130 patient advocacy groups. The involvement of patient advocacy group organizations in each consortium is critical to RDCRN's success. Two of the current RDCRN consortiums are the Rare Lung Diseases Consortium[1167] (RLDC) and the Brittle Bone Disorders Consortium[1168] (BBDC).

To reduce the burden of rare and undiagnosed diseases, RLDC funded a clinical trial to develop a new treatment for a rare lung disease called lymphangioleiomyomatosis (LAM). The trial resulted in the development of a treatment called sirolimus (Rapamune), which stabilized patients' lung function, reduced symptoms, and improved quality of life after 12 months of intake. In 2015, FDA approved the supplemental New Drug Application for Sirolimus (Rapamune), based on results from the RLDC-funded Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) Trial. Sirolimus is now the first treatment ever approved for LAM.[1169]

BBDC is a multidisciplinary collaboration supported by NIAMS, NIDCR, NCATS, and NICHD. It focuses on understanding and providing better treatment options for rare diseases characterized by bone fragility and fractures. The consortium's goals include better understanding of genetic forms of osteogenesis

[1163] https://www.genome.gov/13013963/nhgri-participation-in-the-nih-common-fund/.
[1164] https://gateway.undiagnosed.hms.harvard.edu/static/start.html.
[1165] https://www.nih.gov/news-events/undiagnosed-diseases-network-launches-online-application-portal.
[1166] https://ncats.nih.gov/rdcrn/about.
[1167] https://www.rarediseasesnetwork.org/cms/rld/.
[1168] https://www.rarediseasesnetwork.org/cms/BBD.
[1169] https://ncats.nih.gov/pubs/features/lAM-treatment-sirolimus-fda-approved.

imperfecta, known as brittle bone disease, as well as expanding treatment options, developing quality-of-care measures, and training the next generation of physicians and scientists in genetic bone diseases.[1170]

Other Research into Rare and Undiagnosed Diseases

To advance knowledge about rare and undiagnosed diseases, NIAID IRP investigators examined the clinical aspects of pediatric mastocytosis, a rare disease that affects the skin and multiple organs, to develop practical guidance for disease management. Investigators determined that in patients with pediatric mastocytosis, serum tryptase correlated with bone marrow mast cell burden and that there was a significant relationship between clinical resolution and the percentage decrease in tryptase levels. These findings provide further guidance in the management of children with mastocytosis and highlight the need for tailoring WHO criteria in the pediatric population.[1171]

NIAID researchers and their collaborators also studied idiopathic systemic capillary leak syndrome (SCLS), a rare but severe disorder characterized by acute and recurrent episodes of vascular leak, in a cohort of children. The researchers administered intravenous or subcutaneous immunoglobulin to four patients , none of whom experienced disease recurrence since the treatment began. This study adds to our knowledge of a sporadic blood disorder that presents differently in children and suggests that immunoglobulin therapy may be a well-tolerated and successful treatment for preventing recurrent episodes in children.[1172]

Working toward the development of treatment for rare diseases, NIAMS supported research for treating epidermolysis bullosa (EB), an inherited skin disease. EB is a family of inherited disorders, caused by genetic defects in structural proteins of the skin and mucous membranes, leading to epidermal and mucosal fragility and blistering. Currently, the standard of care for EB is palliative wound care and skin grafting to chronic wounds. In two recent studies, NIAMS-supported research demonstrated the feasibility of using iPSCs, with either genome editing technologies or spontaneous correction of mutations in revertant mosaicism, to develop patient-specific cell-based therapies for EB and other rare heritable diseases of the skin. Together, these studies make substantial progress toward personalized iPSC-derived medicine.[1173]

Rare Disease Day

Rare Disease Day takes place worldwide, typically on or near the last day of February each year, to raise awareness among policymakers and the public about rare diseases and their impact on patients'

[1170] https://www.rarediseasesnetwork.org/cms/bbd.
[1171] https://www.ncbi.nlm.nih.gov/pubmed/26044856.
[1172] https://www.ncbi.nlm.nih.gov/pubmed/25713284.
[1173] https://www.ncbi.nlm.nih.gov/pubmed/25429056.

lives. Each year, NCATS and the NIH Clinical Center sponsor Rare Disease Day at NIH to raise awareness about rare diseases, the people they affect, and research collaborations that are making a difference.[1174]

Microbiome

The body of a healthy human adult is home to an enormous bacterial ecosystem, called the human microbiome, with bacterial cells outnumbering human cells 10 to 1. The human microbiome is fundamental to the maintenance of human health. Despite misconceptions that associate all bacteria with disease, most of this natural bacterial flora is composed of commensal—or beneficial—species that actually perform necessary functions, such as digesting certain nutrients in the intestines. However, evidence indicates that dysregulated ("dysbiotic") microbial communities can contribute to a wide range of diseases and conditions, including obesity, diabetes, cancer, and autoimmune diseases.

Summary of NIH Activities

We now have a good understanding about the diversity and distribution of human-associated microbial communities. However, the biology of the microbiome, how it interacts with the host, and how the host responds to the resident microbiota remains unmapped territory. To further clarify the principles and mechanisms that govern the dynamics of host-associated microbial communities, many ICs, including NIGMS, NIEHS, NHGRI, NIAID, NHLBI, NIDDK, NCCIH, and NIDCR, as well as the OD Common Fund, support genetic, physiological, and ecological studies. This section includes an overview of some of NIH's microbiome research; other NIH activities relating to microbiome research are found throughout other sections this chapter.

Trans-NIH Activities

Through the Common Fund and research by NIH intramural labs, the Human Microbiome Project[1175] (HMP) aims to discover the composition of the microbial communities in different parts of the human body and understand how these communities are associated with human health and disease.[1176] The first of these goals—characterizing the composition of the microbiome in healthy people—was addressed in the first phase of the HMP, which began in 2007. The second phase, which began in FY 2013, is addressing the second HMP goal: enriching our understanding of how changes in the microbiome correlate with disease. This phase is focused on activities to create the first integrated datasets of biological properties from both the microbiome and the host, using high-throughput multi-omics (transciptomics, proteomics, metabolomics) technologies.

[1174] https://directorsblog.nih.gov/2014/02/27/rare-disease-day-were-joined-together-by-this-common-thread/.
[1175] https://commonfund.nih.gov/hmp.
[1176] http://commonfund.nih.gov/hmp/index.

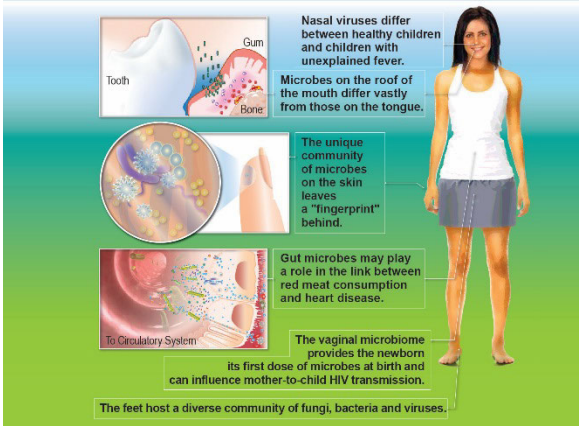

Figure 54. The Human Microbiome Project examines several body sites, increasing knowledge of the impact of microbes in association with both health and disease. Credit: A Decade of Discovery—The NIH Roadmap and Common Fund.

The second phase of HMP is called the Integrative HMP[1177] (iHMP), because it reflects the program's goal of creating an integrated dataset of multi-omics data from host and microbiome as a community resource. In this phase, the iHMP is using multiple -omics technologies to profile the microbiome and host characteristics in three microbiome-related health conditions—pregnancy and preterm birth,[1178] the onset of inflammatory bowel disease (IBD),[1179] and the onset of type 2 diabetes[1180]—described in detail in the iHMP marker paper published in 2014.[1181] Each of these study groups has engaged in providing new computational tools and integrative molecular perspectives on microbial activity during dysbiosis. By creating these multi-omics data resources, the iHMP has opened up new opportunities for data integration in the human microbiome. Planning for the data integration/testing activities began in earnest at the first annual iHMP Consortium meeting, in June 2014. From 2008 to 2014, 475 papers cited HMP support, showing prolific growth of research in this field. As the microbiome research field matures, individual NIH ICs have begun to conduct microbiome research independently, with several updates included below.

The Trans-NIH Microbiome Working Group (TMWG), established in 2012, is chaired by HMP staff and consists of extramural staff from 19 NIH ICs. It meets monthly, serving as a forum for staff to plan workshops, discuss important meetings, develop FOAs, and discuss other activities relevant to NIH support of microbiome research. TMWG published a commentary in an October 2014 issue of *Cell,* calling for support of interdisciplinary research, analytical rigor, standardization, and policy development to advance this rapidly developing field.[1182] In FY 2015, a trans-NIH FOA that TMWG had developed was published.[1183]

[1177] http://www.hmp2.org/.
[1178] https://projectreporter.nih.gov/project_info_description.cfm?aid=8731192&icde=35427311.
[1179] https://projectreporter.nih.gov/project_info_description.cfm?aid=8731194&icde=35427274.
[1180] https://projectreporter.nih.gov/project_info_description.cfm?aid=8731193&icde=35427358.
[1181] Integrative HMP (iHMP) Research Network Consortium. *Cell Host Microbe* 2014;16(3):276-89. PMID: 25211071.
[1182] Huttenhower C, et al. *Cell* 2014;159(2):227-30. PMID: 25303518.
[1183] http://www.niaid.nih.gov/news/newsreleases/2015/Pages/skinCommensals.aspx.

The Digestive Tract Microbiome

NIDDK supports research on the community of microbes that naturally inhabit the human intestine—referred to as the gut microbiota or gut microbiome—and its effects on IBD. Identifying the communities of bacteria that populate the intestine and understanding the roles they play in human health and disease is crucial to developing new treatments for adult and pediatric forms of IBD. In September 2014, NIDDK hosted a workshop to advance understanding of how host physiology and disease pathophysiology are affected by the gut microbiota and to define research needs and opportunities for investigating host–microbiota interactions and their role in disease. Feedback from the workshop was used to develop new initiatives, launched in 2015, encouraging applications for new research in this area. These efforts included an FOA supporting development of a community research resource of microbiome-derived factors modulating host physiology in obesity, digestive and liver diseases, and nutrition,[1184] as well as support of exploratory studies to explore and interrogate functional interactions between the gut microbiome and the host in obesity, digestive and liver diseases, and nutrition.[1185]

NIDDK works closely with NHGRI and other NIH ICs to support research through HMP, which is contributing to advancing our understanding of IBD and the role of gut microbial factors. The Inflammatory Bowel Disease Multi'omics Database (IBDMDB), part of HMP's second phase, is a multi-institutional effort to understand how the human gut microbiome changes over time in adults and children with IBD. The overall goal is to provide translationally actionable targets for IBD therapy or diagnosis.[1186]

In a study released in 2014, NIDDK-funded scientists identified several genes and types of bacteria that are associated with inflammatory diseases in the human gut, suggesting that people with IBD have a particular microbial and genetic signature that could provide targets for improved diagnosis and therapy.[1187] Also in 2014, another group of researchers, funded by NIAMS, identified the bacteria associated with IBD by determining which bacteria are coated with a type of antibody, called immunoglobulin A (IgA), that the body produces to protect itself from foreign substances.[1188] Together, these findings offer important clues that may lead to better diagnosis and management of IBD.

It is estimated that the human oral microbiome consists of over 600 unique species of bacteria, all functioning together with the host to maintain oral, digestive, and immune system health. NIDCR supports a variety of research strategies to better understand how the oral microbiome keeps our mouths healthy and how and why changes in the oral microbiome result in oral and systemic disease. The oral microbiome includes elusive microorganisms called uncultivables because they cannot be grown and studied in the laboratory. They represent the next frontier in oral microbiology because their roles in health and disease are unknown. NIDCR-funded research has enabled the cultivation of an oral

[1184] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-012.html.
[1185] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-013.html.
[1186] https://ibdmdb.org/.
[1187] Haberman Y, et al. *J Clin Invest* 2014;124(8):3617-33. PMID: 25003194.
[1188] Palm NW,et al. *Cell* 2014;158(5):1000-1010. PMID: 25171403.

microbe called TM7x bacterium in the laboratory for the first time. TM7x's distinct characteristics, previously unobserved in the human microbiome, showed that this bacterium requires the presence of another bacterium, *Actinomyces*, to survive. TM7x also displays potential immune suppression abilities, which may contribute to the initiation or progression of periodontitis.[1189]

NCI funds research to examine whether oral microbiome profiles are associated with risk of oral, pharyngeal, laryngeal, and esophageal squamous cell cancers, as well as the impact of alcohol and tobacco use on the oral microbiome. Similarly, another NCI project will test whether changes in oral microbiome contribute to the development of esophageal adenocarcinoma and whether these changes are present in buccal cell samples collected before cancer diagnosis. The study may lead to microbial biomarkers that can be used for early detection of esophageal adenocarcinoma.

The Microbiome and Infection

The role of the microbiome in susceptibility, risk, and progression of immune-mediated and infectious diseases; response to therapeutic interventions; and emergence and spread of drug resistance is of great interest to NIH. One of the high-priority research areas in this field is the creation, using a systems biology framework, of models of the microbiome's function and dynamics that can be used to identify predictive biomarkers of health, disease, and response to therapeutic intervention.

Skin, the primary interface between the host and the environment, is home to trillions of microorganisms that play an important role in tissue homeostasis and local immunity. NIAID IRP investigators demonstrated that the various microbes that naturally colonize the skin may influence skin immunity and that immune cells in the skin tissue are poised to sense and respond to alterations in microbial communities. These findings have profound implications for understanding tissue-specific immunity and pathologies.[1190]

Beginning in 2014, NIAID is supporting a Phase I, randomized, placebo-controlled, double-blind study to evaluate a novel antibiotic, CRS3123, for treating *C. difficile* infection. The primary goal of this study is to determine the safety and tolerability of multiple escalating oral doses of CRS3123 in healthy adults. Because significant alterations in the gut microbiome are associated with susceptibility to *C. difficile* infection, this clinical trial includes a substudy to determine what impact CRS3123 administration has on the gut microbiota.[1191]

In mouse studies, NIAID IRP scientists demonstrated that a single, transient encounter with a gut pathogen, *Yersinia pseudotuberculosis* (*Yp*), can trigger long-term consequences that compromise the immune system's balance, impair immune function, and cause persistent inflammation in the gut-associated adipose (fat) tissue. Microbes in the intestinal tract, part of the body's naturally occurring microbiome, maintain an immune imbalance even after the initial infection has been resolved. As a result, migratory dendritic cells are shunted from mesenteric lymph nodes, so mucosal immune

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[1189] He X, et al. *Proc Natl Acad Sci USA* 2015;112(1):244-9. PMID: 25535390.
[1190] Naik S, et al. *Nature* 2015;520(7545):104-8. PMID: 25539086.
[1191] https://clinicaltrials.gov/ct2/show/NCT02106338.

functions are persistently compromised. This study provides a framework to understand how infections can induce a breakdown of tissue immune homeostasis, contributing to disease (e.g., allergy, chronic inflammatory disorders such as Crohn's disease) later in life.[1192,1193]

Researchers studying intestinal bacteria in newborns have characterized the gut bacteria of premature infants who go on to develop sepsis, a serious and potentially life-threatening condition caused by bacteria in the bloodstream. The findings indicate that sepsis-causing bacteria may be found in infants' guts but that they are not always present. These findings suggest new strategies for the early detection and prevention of severe bloodstream infections. These strategies might include better surveillance, decolonization treatments, and a focus on hygiene to prevent transmission of these dangerous bacteria between and within premature infants.[1194]

The interplay between environmental exposures, the respiratory tract microbiome, and immune responses related to asthma and other respiratory diseases is not well understood. In 2015, NIEHS began funding a project evaluating the impact of traffic-related air pollutants (TRAP) and the respiratory microbiome in children. This research aims to characterize bacterial community profiles of the lower respiratory tract microbiome in children ages 12–15 and to determine the association between childhood exposure to TRAP and the microflora in the lower respiratory tract of these children. A multidisciplinary team of researchers is involved.[1195]

Minority Health and Health Disparities

Disparities in health care, which hinder efforts to improve the nation's health, represent one of the most persistent public health challenges in the U.S. Despite scientific and technological advancements, some populations in the U.S. still face disparities in health status and health care delivery. These disparities in health are most visible in racial and ethnic minority groups, individuals from socioeconomically disadvantaged backgrounds, and people living in medically underserved areas, including rural communities.

According to the 2014 U.S .Census, approximately 38 percent of the nation's population belongs to a racial or ethnic minority group.[1196] NIH has devoted considerable resources to understanding minority health[1197] and the root causes of health disparities[1198] affecting racial and ethnic minorities and other

[1192] Fonseca DM, et al. *Cell* 2015;163(2):354-66. PMID: 26451485.
[1193] http://www.niaid.nih.gov/topics/immuneSystem/Pages/BelkaidCellFeature.aspx.
[1194] Carl MA, et al. *Clin Infect Dis* 2014;58(9)1211-8. PMID: 24647013.
[1195] https://projectreporter.nih.gov/project_info_description.cfm?aid=8968715&icde=35420967.
[1196] https://www.census.gov/newsroom/press-releases/2015/cb15-tps16.html.
[1197] NIH defines minority health research as the scientific investigation of distinctive health characteristics and attributes of minority racial and/or ethnic groups who are usually underrepresented in biomedical research in order to understand population health outcomes. https://hdpulse.nimhd.nih.gov/.
[1198] NIH defines health disparities research as a multidisciplinary field of study devoted to gaining greater scientific knowledge about the influence of health determinants, understanding the role of mechanisms, and determining

disadvantaged groups. As a result of these efforts, a complex web of interconnected and overlapping factors (e.g., biological, behavioral, environmental, societal) have begun to be identified. 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 factors such as physiology, behavior, and gene expression. For example, research shows that poverty and lack of education correlate with poor health and lower life expectancy. Furthermore, it is now understood that discrimination based on racial, ethnic, and linguistic differences not only triggers biological stress but also creates a barrier to accessing high-quality health care. Some groups of people are genetically more susceptible to certain diseases, and when this inherited biological vulnerability combines with adverse social and environmental factors (e.g., poor diet, pollution, economic stress), these groups exhibit poorer health outcomes.

Confronting the interrelated factors that contribute to the existence of health disparities is at the heart of NIH's vigorous efforts to make scientific advances that will translate into effective prevention and treatment interventions.

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 has incorporated the goals of improved health for all Americans and the elimination of health disparities into its support of biomedical and behavioral research, research training, research capacity-building, outreach, and research and health information dissemination.

NIH funding for minority health was estimated to be $2,514 million in FY 2014 and $2,538 million in FY 2015. The funding for health disparities was estimated to be $2,734 million in FY 2014 and $2,538 million in FY 2015.[1199] NIMHD is the lead IC in this area, but many of these activities are multidisciplinary collaborations involving several ICs, often with contributions from other Federal and non-Federal organizations. NIH funding of minority health and health disparities research in specific health areas is illustrated in other sections of this chapter, and a full update on the NIMHD Centers of Excellence is presented in Chapter 4. Additional updates on NIH activities are illustrated below.

Fostering Research on Minority Health and Reducing Health Disparities

From workshops to research resources across NIH, several efforts specifically targeted toward developing a biomedical research endeavor that better serves racial and ethnic minorities are underway. In April 2015, ORWH hosted a workshop on the unique health challenges faced by women of color. The workshop featured presentations by NIH intramural and extramural scientists who provided insight on

how this knowledge is translated into interventions to reduce or eliminate health disparities. https://hdpulse.nimhd.nih.gov/.

[1199] https://report.nih.gov/categorical_spending.aspx.

the disparities involved in a wide range of conditions, including cancer, cardiovascular disease, the risk of HIV infection, and disability in an aging population.[1200]

Without participant diversity in clinical research, the true benefits and risks of new therapies for diverse groups may not be fully understood. By increasing recruitment diversity, researchers' knowledge of pathophysiology and treatment effects will also increase, potentially leading to long-term health benefits and outcomes. NIMHD launched the Randomized Recruitment Intervention Trial (RECRUIT) to test a recruitment intervention to increase racial and ethnic diversity in clinical trials. The sites randomized to the intervention work with the RECRUIT team to enhance and refine recruitment methods to increase the proportion of racially and ethnically diverse participants, compared with the sites randomized to the control. RECRUIT's ancillary aims include describing mediating factors affecting success.[1201]

Affecting Clinical and Community Practice

As described in Chapter 2, postclinical translational research and dissemination of clinical research findings to the broader community is a vital part of the NIH research continuum. To support this vital step, NIH has initiated health disparities and minority health–related programs.

In 2015, NHLBI created a program to support research into accelerating the adoption of guideline-based recommendations into clinical care for populations with health disparities. Health care professionals, particularly those who serve minority and low-income patients, often face cultural, economic, and other barriers to adopting clinical practice guidelines into routine care. The aim of this new NHLBI program is to help identify multilevel strategies that increase guideline adoption for care related to heart, lung, blood, and sleep problems in minority and low-income populations.[1202]

To disseminate health information and promote health by considering the specific needs of a community, NIMHD funded a multilevel health promotion program in African American churches to examine the role of church-based health interventions in reducing health disparities. By using community-based participatory principles, this study conducts a needs assessment survey with 10 churches and 10 health- and community-based organizations to identify health conditions that disproportionately affect community members, as well as possible intervention strategies. The findings will then be followed by the development of culturally/religiously tailored, multilevel health promotion interventions that engage church health liaisons and health providers in promoting prevention, screening, and links to care. This model could have a significant public health impact by providing a faith community engagement model for implementing scalable, wide-reaching socio-ecological interventions.[1203]

[1200] Plank-Bazinet JL, et al. *J Womens Health* 2016;25(1):4-10. PMID: 26771559.
[1201] https://projectreporter.nih.gov/project_info_details.cfm?aid=8873995&icde=35579581.
[1202] https://grants.nih.gov/grants/guide/pa-files/PAR-15-279.html.
[1203] https://projectreporter.nih.gov/project_info_description.cfm?aid=8585091&icde=35579482.

NLM is also focusing efforts at the community level, establishing a program to support the development of information resources to reduce health disparities by bringing useful, usable health information to health disparity populations and their health care providers. Four new awards were made in FY 2015 to support the development of information resources tailored to needs of a number of underserved populations.[1204]

The Trans-NIH American Indian and Alaska Native Health Communications and Information Work Group,[1205] led by NIAMS, partners with the Indian Health Service (IHS) and the Administration on Aging's Administration for Community Living to distribute a quarterly electronic newsletter called *Honoring Health: Resources for American Indians and Alaska Natives*, launched in 2015.[1206] Each issue features a different health topic of interest to Native communities, designed to increase awareness of health information and resources from NIH and other Federal agencies.

Maternal and Child Health

Improving the health and well-being of mothers and children is a public health goal, since those factors affect the health, wellness, and quality of life of current and future generations and determine the future of public health.[1207] In 2015, NIMHD funded research that supports community-based decision-making, aiming to eliminate disparities in maternal and child health. Through this research, a Community Priority Index (CPI) and accompanying software have been developed to facilitate prioritization of community health disparity issues. The CPI is the first instrument of its kind that can be used to prioritize community health issues by combining subjective and objective data from community needs assessments into a single measure. Providing public health practitioners and community development advocates with reliable measures for priority-setting is a necessary step toward fostering accountability in the decision-making process in community settings.[1208]

NIMHD also funded research that supports the use of innovative communication technology to improve the preconception health of young African American women. The goal is to improve the preconception health of African American women ages 18–25 by using an Internet-based health communication system that provides personalized health information through an animated avatar. The intervention includes personal stories from other women who have received the intervention, provided by an automated indexing algorithm that selects the stories most relevant to a user's situation and her readiness to change her health behavior.

NICHD is committed to identifying key challenges in child and maternal health and closing the disparity gaps. To uphold its commitment, NICHD conducted research to determine whether current standards may misclassify minority fetuses as growth-restricted. Fetal growth restriction is a medical term used to

[1204] http://grants.nih.gov/grants/guide/rfa-files/RFA-LM-17-002.html.
[1205] https://www.niams.nih.gov/about-niams/working-groups-and-committees/nih-american-indian-alaska-native-health-communications.
[1206] http://www.niams.nih.gov/News_and_Events/AIAN_Honoring_Health/.
[1207] https://www.healthypeople.gov/2020/topics-objectives/topic/maternal-infant-and-child-health.
[1208] https://report.nih.gov/UploadDocs/NIH%20Pediatrics%20Research%20Initiative%20Report%202015.pdf.

describe fetuses that do not keep up with growth milestones appropriate to their stage of development. NICHD researchers sought to compile standards that more accurately reflect the best fetal growth during healthy pregnancies among the most common racial and ethnic groups in the U.S. The fetal growth data from more than 1,700 women with healthy pregnancies at 12 hospitals in the U.S. revealed significant differences among fetal growth in the different racial and ethnic groups after the 20th week of gestation. The results indicated that current standards for ultrasound evaluation of fetal growth might lead to misclassification of up to 15 percent of fetuses of minority mothers as being too small. The inaccurate standards may result in unnecessary tests and stress for these women.[1209]

In 2015, NICHD-funded researchers published a study examining racial disparities in managing children's pain. This research involved the review of a national database of medical records for nearly 1 million emergency department visits by children who were diagnosed with appendicitis. Results indicated that African American children diagnosed with acute appendicitis in emergency departments are significantly less likely than other children to receive any pain medication, including any opioid medication for severe pain. Appendicitis pain appeared to be untreated in close to half of all African American children studied, with only 57 percent receiving any medication for pain. The investigators called for more research to inform the design of interventions to improve pain management for all pediatric patients and to eliminate the difference in care for young African American patients in pain. [1210]

HIV/AIDS

According to CDC, African Americans are the racial and ethnic group most significantly affected by HIV, accounting for 45 percent of U.S. HIV diagnoses in 2015.[1211] In 2014, NIMHD funded a study aiming to reduce the risk of HIV/AIDS infection among African American men. The study tested the efficacy of a theory-based, gender-specific, contextually appropriate HIV/STD risk-reduction intervention with increasing and consistent condom use, identifying theoretical mediators that account for the interventions' effects, and testing a strategy to enhance the longevity of the intervention's effects.[1212]

Because HIV/AIDS poses a threat to public health, numerous research projects focused on reducing and eliminating the disease are being conducted nationally. However, as with other research studies, ethics play a significant role in how this type of research is conducted. This is particularly important in minority groups, which might include more sensitive or vulnerable portion of the population. NIMHD has performed a project using a mixed-methods approach to examine the ethical issues regarding the participation of lesbian, gay, bisexual, and transgender (LGBT) youth under the age of 18 in HIV prevention research, with a particular emphasis on the requirement for parental consent. This project has collected data from LGBT youth by using online focus groups, surveys, and responses to a hypothetical clinical trial to examine perceived risks and benefits of participation in HIV prevention

[1209] Buck GM, et al. *Am J Obstet Gynecol* 2015;213(4):449.e1-449.e41. PMID: 26410205.
[1210] Goyal MK, et al. *JAMA Pediatr* 2015;169(11):996-1002. PMID: 26366984.
[1211] https://www.cdc.gov/hiv/group/racialethnic/africanamericans/.
[1212] https://projectreporter.nih.gov/project_info_details.cfm?aid=8587440&icde=35331083.

research.[1213] More information on NIH research HIV/AIDS research efforts is included in the infectious disease and biodefense section of this chapter.

Asthma

The prevalence and morbidity of childhood asthma varies among Latinos in the U.S., depending on their country of origin/heritage. One NIMHD-funded study analyzed 5,493 Latinos, using genome-wide data to determine participants' proportion of African, European, and Native American ancestry. Results indicate that differences in genetic ancestry can partially explain disparities in asthma susceptibility and lung function among Latinos.[1214] Another NIMHD-funded study examined the effects of prenatal exposure to community violence and physical stressors (air pollution) on repeated wheeze in 708 urban children followed to the age of 2. The findings suggest that both factors could affect respiratory health in urban children.[1215,1216]

NHLBI launched the Asthma Empowerment Collaborations to Reduce Childhood Asthma Disparities initiative in 2015. The program will evaluate comprehensive asthma care programs for children at high risk of poor asthma outcomes, with a focus on poor and minority children. Eligible programs must include four separate interventions focusing on the home environment, family issues, community issues, and medical care. For example, an eligible program might involve (1) assessing and reducing allergens at home; (2) training parents in disease management; (3) working with community leaders to reduce asthma triggers in school buildings; and (4) ensuring that local medical practitioners adhere to asthma clinical practice guidelines.[1217]

The NHLBI-supported Best African American Response to Asthma Drugs (BARD) trial is testing the efficacy of different treatment approaches in African American children and adults with asthma and is assessing the effect of genetics on treatment response. This multicenter trial will enroll approximately 500 African American children and adults with asthma to see how they react to the different therapies and how their genetics affect those reactions.[1218]

Diabetes

Diabetes is more common among all members of racial and ethnic minorities than among Whites. CDC estimates that 13 percent of Hispanics/Latinos age 20 and older have been diagnosed with diabetes, as have 9 percent of Asian Americans.[1219] When undiagnosed cases of diabetes are also considered, the rates may be much higher: NIDDK-funded researchers using NHANES to look at diabetes prevalence

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[1213] https://projectreporter.nih.gov/project_info_description.cfm?aid=8934138&icde=35580101.
[1214] Pino-Yanes, M, et al. *J Allergy Clin Immunol* 2015;135.1:228-235. PMID: 25301036.
[1215] https://projectreporter.nih.gov/project_info_description.cfm?aid=8706705&icde=35579081.
[1216] Chiu, YH, et al. *J Allergy Clin Immunol* 2014;133(3):713-22. PMID: 24200349.
[1217] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-001.html.
[1218] http://www.nhlbi.nih.gov/news/press-releases/2014/nih-study-seeks-to-improve-asthma-therapy-for-african-americans.
[1219] https://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.

rates, including undiagnosed diabetes, found that nearly 21 percent of Asian Americans have diabetes. Asian Americans also had the highest proportion of undiagnosed diabetes (51 percent) among all ethnic and racial subgroups studied and were likely to develop type 2 diabetes at a lower BMI than other groups.[1220]

Ongoing research is trying to tease out what might underlie these racial and ethnic differences. An investigation of the association of arsenic metabolism with diabetes in the Strong Heart Study—a population-based prospective cohort study of cardiometabolic diseases among three American Indian communities—showed a prospective association between arsenic metabolism and increased incidence of diabetes.[1221]

NIH also funds research on interventions to help prevent or treat diabetes in racial and ethnic minorities. To help prevent the development of type 2 diabetes in Hispanic women with prior gestational diabetes, an NIMHD-funded investigation developed a mobile phone app based on the Diabetes Prevention Project (DPP) to promote self-efficacy and behavioral change. This research has the potential to improve health outcomes for many women from an underserved population that is at high risk of developing type 2 diabetes.[1222]

Following the successful trial of the NIDDK-led DPP in 2002, the translation of this lifestyle intervention to community settings has been a major public health focus, with significant support from CDC through the National Diabetes Prevention Program (NDPP). Although NDPP has been shown to be effective for enrolled participants, resulting in weight loss of 5–7 percent, independent of setting and population group, there are striking disparities in engagement. Participation rates are particularly low for Black and Latino men (below 20 percent). Men of color are more likely than their White counterparts to face significant disadvantages, experiencing higher rates of life-threatening diabetes-related complications. Given the disproportionate burden of diabetes and its complications for disadvantaged groups, targeted diabetes prevention programming is a crucial component of public health planning. NIDDK has therefore funded a translational, cluster-randomized trial of NDPP in 16 sites, testing culturally tailored approaches to recruit, engage, and retain men from disadvantaged communities in type 2 diabetes prevention. Another NIDDK-funded project is testing a culturally tailored DPP adaptation for immigrant Latino workers in farm work and other low-wage industries.

NIDDK's Translational Research for the Prevention and Control of Diabetes and NIDDK Centers for Diabetes Translation Research fund type 2 translational research (from bedside to practice and the community) based on past successful diabetes clinical trials, including projects to reduce the cost and increase the availability of lifestyle interventions to prevent diabetes, based on the intervention found highly effective in the landmark DPP clinical trial. These efforts emphasize ameliorating disparities in diabetes burden and outcomes and addressing health equity (e.g., through a center dedicated to addressing diabetes disparities in American Indian/Alaska native communities; through inclusion of a

[1220] Menke A, et al. *JAMA* 2015;314(10):1021-9. PMID: 26348752.
[1221] Kuo CC, et al. *Diabetes Care* 2015;38(4):620-7. PMID: 25583752.
[1222] https://projectreporter.nih.gov/project_info_description.cfm?aid=8898581&icde=34642868.

national research core for research in Latino communities).[1223,1224,1225] NIDDK's Pragmatic Research in Healthcare Settings to Improve Diabetes and Obesity Outcomes program tests practical, sustainable approaches to improving diabetes and obesity prevention and/or treatment in routine health care settings; its aim is to obtain results that can improve routine healthcare practice and inform policy for the prevention or management of these conditions.[1226]

Findings from an NIMHD study suggest that experiencing more stress is associated with poorer adherence to diabetes medications among low socioeconomic status (SES) adults who were trying to be adherent. Research in the same study found that depression was the primary reason that diabetic adults demonstrated poor adherence to dietary restrictions, but the number of stressors experienced also affected adherence. Experiencing numerous chronic stressors presents barriers to medication adherence that are distinct from associated depressive symptoms.[1227]

To address such problems, NIDDK has funded a project to test the effectiveness of a collaborative model program implemented within six clinics on Chicago's South Side on the quality of diabetes care and outcomes. This multifactorial intervention incorporates training clinicians on culturally tailored patient activation, cultural competency, and communication, as well as clinic redesign with input from patient advocates, a quality improvement collaborative, care management, and enhanced community partnerships. The intervention also seeks to increase the number of people with diabetes from underserved populations who access comprehensive care in safety net health centers, through engagement with patient advocates and partnerships with community-based organizations.

Kidney Diseases

African Americans develop end-stage renal disease at rates 4–5 times higher than Whites. Variations in the *APOLI1* gene contribute to a large proportion of this disparity. One NIMHD-funded study is investigating the molecular mechanisms that lead to glomerular injury from the *APOL1* gene variant G1 and how *APOL1* G1 and G2 contribute to end-stage renal disease. Aside from its well-defined role in resistance to African sleeping sickness, little is known about the biology of APOL1 or its role in the kidney. Using a human embryonic kidney cell culture system, the study found that the *APOL1* G1 and G2 risk variants increases cell death through loss of intracellular potassium and induction of stress-activated protein kinase signaling pathways. These results shed new light on how *APOL1* risk variants give rise to disparities in end-stage renal disease and may point the way to targeted therapies.[1228]

NIDDK-funded researchers also found that variations in the *APOL1* gene are associated with increased risk of kidney disease but not cardiovascular disease in African Americans with high blood pressure.[1229]

[1223] https://grants.nih.gov/grants/guide/pa-files/PAR-13-366.html.
[1224] https://grants.nih.gov/grants/guide/pa-files/PA-13-352.html
[1225] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-10-009.html.
[1226] https://grants.nih.gov/grants/guide/pa-files/PAR-13-366.html.
[1227] https://projectreporter.nih.gov/project_info_description.cfm?aid=8685788&icde=35575493.
[1228] https://projectreporter.nih.gov/project_info_description.cfm?aid=9212011&icde=35575757.
[1229] Langefeld CD, et al. *Kidney Int* 2015;87(1):169-75. PMID: 25029429.

This work builds off earlier NIDDK-supported research, which found that African Americans who have chronic kidney disease and two copies of common variants in the *APOL1* gene are twice as likely to progress to kidney failure as people without these high-risk variants. Moreover, African Americans with the high-risk variants also tend to lose kidney function at twice the rate of those without the variant.[1230]

Kidney transplantation is the preferred treatment for patients with end-stage kidney disease. However, disparities in long-term results show 10-year graft survival rates of only 34 percent in African Americans, significantly below the 45 percent survival rate in Whites. Two *APOL1* gene risk variants are associated with worse allograft survival. Kidney disease risk variants in the *APOL1* gene in kidney donors significantly shorten allograft survival, providing strong evidence that donor kidney gene variants affect transplant outcomes. Investigators observed shorter renal allograft survival after transplantation from donors with two *APOL1* risk variants. Younger recipient age and older donor age had independent adverse effects on allograft survival. This research suggests that rapid genotyping of deceased African American kidney donors for *APOL1* risk variants at organ recovery may improve transplantation outcomes.[1231]

Obesity

While the prevalence of obesity is high among all U.S. population groups, 48 percent of African Americans are obese, followed by 43 percent of Hispanics, 33 percent of non-Hispanic Whites, and 11 percent of Asians.[1232] More than 75 percent of Hispanic women in the U.S. are overweight or obese, and Hispanic children have the highest rates of obesity among any racial or ethnic group in the U.S. One NIMHD-funded study is developing a healthy eating mobile app that offers the ability to create a user-generated grocery list, analyzes nutritional value and cost of food, and promotes USDA's MyPlate visual method. The app is tailored toward Hispanics, incorporating Spanish language, culturally tailored shopping suggestions, educational and motivational text messages, and peer support via social media.[1233]

An NIMHD-funded study found that low birth weight may disrupt central nervous system regulation of adult BMI. The researchers collected data from 2,215 African American women from the Black Women's Health Study and genetic data on 20 BMI-associated loci and self-reported data on birth weight, weight at age 18, and adult weight.[1234] Three single-nucleotide polymorphisms (SNPs) showed a significant interaction with birth weight and BMI. Among women with low birth weight, these SNPs were correlated with higher BMI at age 18 and adult weight. All three SNPs are highly expressed in the central nervous system, suggesting that low birth weight may disrupt mechanisms of central nervous system body weight regulation.

[1230] Parsa A, et al. *N Engl J Med* 2013;369(23):2183-96. PMID: 24206458.
[1231] https://projectreporter.nih.gov/project_info_description.cfm?aid=8890212&icde=34703229.
[1232] https://www.cdc.gov/obesity/data/adult.html.
[1233] https://projectreporter.nih.gov/project_info_description.cfm?aid=8739671&icde=34703265.
[1234]https://projectreporter.nih.gov/project_info_details.cfm?aid=8790907&icde=36452040&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

Online programs encouraging young African American girls to develop healthy diet and physical activity behaviors before adolescence could help reduce the risk of obesity and related diseases later in life. A recent NIMHD-funded study developed an animated, 8-episode interactive online comic. The study will assess whether girls who participate in the online program maintain a stable BMI percentile and whether girls in the participant group have higher fruit, vegetable, and water consumption; more minutes of moderate to vigorous physical activity; and fewer minutes of sedentary activity than girls in the comparison or wait-list control groups immediately after the intervention and 3 months later.[1235]

The Lifestyle Interventions for Expectant Moms (LIFE-Moms) consortium, led by NIDDK, in collaboration with NHLBI, NICHD, NCCIH, ORWH, and OBSSR, continued its clinical trials of several different interventions to improve weight and metabolic outcomes for women and their children. The LIFE-Moms consortium has emphasized recruitment from disproportionately affected minorities and low-SES populations. For example, in one study, researchers continued testing a program designed to improve diet and physical activity in socioeconomically disadvantaged African American women with obesity, during and after pregnancy, using an existing national home visiting program. Because nearly half of U.S. women of childbearing age are overweight or obese, and many observational studies have linked overweight/obesity and excessive weight gain during pregnancy to adverse health consequences in both mothers and their offspring, such studies could have important implications for public health.

Obesity is associated with poor cardiovascular health, and increasing physical activity is essential to reducing rates of obesity. Latinos report high rates of inactivity and related health conditions, including obesity and diabetes. An NINR-funded randomized control trial of an individually, linguistically, and culturally tailored physical activity intervention was developed for a group of Latina women. The intervention included materials mailed out for six months at regular intervals. Six months after the intervention ended, participants were contacted again. They reported significantly higher levels of moderate to vigorous physical activity 12 months from the start of the intervention. This intervention's effectiveness in promoting physical activity in Latinas suggests a potential for broad impact in improving health outcomes for a minority population.[1236]

Stroke and Hypertension

Stroke is one of the leading causes of death in the U.S., and minorities have higher stroke risks, stroke occurrence at an earlier age, and, for some groups, more severe strokes than non-Hispanic Whites do.[1237] Studies have shown that higher prevalence of risk factors, lower SES, and health care system challenges for minority patients may contribute to stroke disparities. Stroke poses a significant burden on minority health, as it increases the risk of mortality, lost wages, and disability.

To close stroke disparity gaps, NINDS is supporting research to develop and test culturally tailored interventions that address major contributors to stroke disparities. This Institute has been funding four

[1235] https://projectreporter.nih.gov/project_info_description.cfm?aid=8687994&icde=34703245.
[1236] Marcus BH, et al. *Am J Prev Med* 2015;48(2):179-82. PMID: 25442225.
[1237] Trimble B, et al. *Neurol Clin* 2008;26(4):1177–1190. PMID: 2621018.

regional programs since 2012, including clinical trials of interventions to improve blood pressure control, effectiveness studies testing novel approaches to the delivery of care (e.g., mobile health technologies and translational care), and observational studies to identify and quantify temporal trends in risk factors. The programs, which have also built partnerships with communities and stakeholders such as Kaiser Permanente and the American Heart Association's Get With The Guidelines program, include training/education and community outreach, as well as plans for scaling up and disseminating successful interventions.[1238]

The NINDS-funded Reasons for Geographic and Racial Differences in Stroke (REGARDS) project is a national study focusing on learning more about the factors that increase a person's risk of having a stroke. Scientists have explored the geographical and racial influences on stroke risk in a cohort of approximately 30,000 people, about half of whom lived in the "stroke belt" region of the southeastern U.S. This study has so far produced more than 300 publications that have led to better understanding of stroke disparities in the U.S.[1239]

Hypertension is one of the major risk factors for stroke. To improve control of hypertension among minority populations, NINDS, NHLBI, and PCORI have partnered the Hypertension Disparities Reduction Program Partnership (HDRPP), a new intervention to identify effective strategies. In FY 2015, two studies were funded to compare alternative strategies in primary care settings. One study in Maryland compared a health system-based intervention and a multilevel intervention incorporating a collaborative care team and community health workers. A second project in Alabama and North Carolina compared a process-driven quality improvement approach with a relationship-oriented approach that incorporates community partnerships and peer coaches.[1240]

Cancer

NIH funds several projects seeking to understand and improve diagnosis of cancer in diverse populations. Notably, NCI awarded 53 new five-year grants to researchers across the country to conduct multisite cancer clinical trials and cancer care delivery research studies in their communities.[1241] These NCI Community Oncology Research Program (NCORP) grants support a national network of investigators, cancer care providers, academic institutions, and other organizations that provide care to diverse populations in community-based healthcare practices across the U.S.. The network is designing and conducting trials to improve cancer prevention, cancer control, screening, and post-treatment management, as well as identify and evaluate the critical interventions that reduce cancer risk and incidence, enhance patients' quality of life, and increase access to clinical trials and cancer care delivery research for minority, rural, and other underserved patient populations. The new program has an expanded portfolio of clinical trials and other studies, including an emphasis on cancer care delivery research. Cancer care delivery research within NCORP focuses on diverse and multilevel factors (e.g.,

[1238] https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-12-007.html.
[1239] http://www.regardsstudy.org/.
[1240] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-021.html.
[1241] https://ncorp.cancer.gov/.

social factors, financing systems, processes, technology) that affect access to and quality of care in the community, where most patients receive their care. Efforts to incorporate cancer disparities research into NCORP include delineating the role of organizations in reducing disparities and evaluating financial toxicities in cancer care.

In addition to efforts supported by NCI, NIMHD established and continues to support the Enhancing Minority Participation in Clinical Trials (EMPACT) program.[1242] This project examines an online education and patient navigation program at five NCI-funded cancer centers to improve racial and ethnic minority recruitment into cancer trials. Specific EMPACT activities include a Web portal that offers online training modules for investigators, research staff, referring physicians, and patient navigators; provides resources for recruitment and retention; and serves as communications and information hub, in order to address identified barriers to recruitment and retention of racial and ethnic minorities into therapeutic cancer clinical trials. Moreover, the implementation and evaluation of a pilot patient navigation program is designed to provide data about the potential efficacy of a navigation intervention for minority recruitment.

In addition to developing infrastructure to support enrollment of diverse populations in clinical trials, NIH supports research to determine why some populations are more vulnerable to specific types of cancer than others. For example, investigators at NCI conducted a multistage genome-wide association study of 935 osteosarcoma patients to determine whether germline genetic variation contributed to risk of metastasis, which is the leading cause of death in patients with osteosarcoma, the most common pediatric bone malignancy. The researchers identified a variant of a gene called *NFIB* that was significantly associated with metastasis at diagnosis in patients with European ancestry, as well as in patients with African and Brazilian ancestry. These data suggest that *NFIB* is an osteosarcoma metastasis susceptibility gene.[1243] Additionally, an NIMHD-funded study examined the association between serum vitamin D levels and prostate biopsy results and found that in African American men, vitamin D deficiency was associated with increased odds of prostate cancer diagnosis on biopsy. In both White and African American men, severe vitamin D deficiency was positively associated with higher Gleason grade and tumor stage.[1244]

NIH has also supported research to develop inexpensive point-of-care (POC) platforms to improve screening and diagnoses in resource-limited settings, such as areas with a high percentage of low-SES individuals, rural areas, and LMICs. In 2015, investigators at the NCATS-funded CTSA hub at the University of Miami developed and implemented an innovative community-based approach to increasing cervical cancer screening in Miami's Little Haiti community. The University of Miami team recognized that women in Little Haiti have disproportionately high rates of morbidity and mortality due to cervical cancer, a common observation in many minority and immigrant communities. The researchers determined that this high incidence rate was derived in part from cultural and access barriers to early screening, as well as a lack of understanding of the disease. The team partnered with

[1242] http://empactconsortium.com/.
[1243] Mirabello L, et al. *Cancer Discov* 2015;5(9):920-31. PMID: 26084801.
[1244] Murphy AB, et al. *Clin Cancer Res* 2014;20(9):2289-99. PMID: 24789033.

community health workers to create an outreach and education program run by members of the community to make cervical cancer screening more culturally acceptable and locally accessible. In addition, a new and simpler diagnostic test enabled women to conduct cervical self-sampling for HPV (the primary cause of cervical cancer) outside a clinical setting.[1245]

Furthermore, NIBIB supported research to develop new POC technologies to diagnose multiple types of cancer. The digital diffraction diagnosis (D3) system is a platform for POC diagnosis, especially in resource-limited settings, that uses microbeads to generate unique diffraction patterns, which can be acquired by smartphones and processed by a remote server.[1246] The D3 platform was applied to molecular profiling of breast cancer cells and to screen for precancerous or cancerous cells in cervical specimens. In this phase of development, the immunobeads target genetic biomarkers for cancer, indicate level of expression, and help determine the most effective therapy. The assay takes 40 minutes and costs less than $2. In a study of 25 patients with abnormal Pap smears, the three-antibody screen showed good agreement with pathology assessment. Finally, NCI and NIBIB have invested significant resources to create the Affordable Cancer Technologies program to support the development and validation of low-cost, POC technologies with the potential to increase early detection, diagnosis, and no-invasive or minimally invasive treatment of cancer in LMICs.[1247] The program supports precommercial technology adaptation from the bench to the bedside, with the goal of inducing a market shift toward affordable, resource-appropriate interventions in LMICs.

Eye, Skin, and Dental Concerns

In glaucoma, degeneration of the optic nerve causes blindness as signals from the eye can no longer reach the brain. Glaucoma prevalence is 4–8-fold higher in African Americans than in Whites. The focus of the African Descent and Glaucoma Evaluation Study (ADAGES) is to evaluate biologic and genomic risk factors of the disease. Eye anatomy and fluid drainage affect a key risk factor for glaucoma-elevated intraocular pressure (IOP). ADAGES investigators found that glaucoma patients of African descent with higher IOP were more likely to develop visual field loss than patients of non-African descent with similar IOP measures were. ADAGES investigators also used genetic analysis of ethnicity to determine participants' biogeographic ancestry and found ancestry-related size differences in the optic disc, the vulnerable structure where the optic nerve exits the eye.[1248]

Despite significant improvements in oral health for the population as a whole, oral health disparities associated with race, ethnicity, SES, gender, age, and geographic location persist in the U.S. In FY 2015, NIDCR continued its investment to reduce oral health disparities, with a new initiative, the Multidisciplinary and Collaborative Research Consortium to Reduce Oral Health Disparities in Children. The Institute awarded more than $7 million in first-year funding for 10 grants aimed at identifying the best methods of eliminating inequities in access to care and improving the oral health of underserved

[1245] Kobetz E, et al. *Trials* 2017;18(1):19. PMID: 28086983.
[1246] Im H, et al. *Proc Natl Acad Sci USA* 2015;112(18):5613-8. PMID: 25870273.
[1247] https://www.cancer.gov/about-nci/organization/cgh/blog/2014/low-cost-technologies.
[1248] Khachatryan N, et al. *Am J Ophthalmol* 2015;159(4):777–787.e1. PMID: 4361282.

children. This work will help communities identify the best ways to reduce oral health disparities and inequities of underserved children by increasing access to care and providing innovative health promotion and disease prevention strategies.[1249]

NIDCR suggests that access to preventive oral health services (POHS) would be increased if such services could be provided by physicians and nurses in communities with an insufficient dental workforce. A recent study linking Medicaid claims of kindergarten students with public health surveillance data in North Carolina supports this recommendation. Kindergarten students with four or more POHS visits had lower numbers of decayed, missing, and filled teeth than students with no visits. However, there was no difference in the numbers of teeth with untreated decay, demonstrating the need for these children to have regular dental care.[1250]

Atopic dermatitis is a chronic skin disease and is most common in children. NIAMS supported research to determine the genetic variants associated with atopic dermatitis in African American patients. Results indicated that two mutations in the gene filaggrin-2 *(FLG2)*, which is closely related to the *FLG* gene, are associated with more persistent atopic dermatitis in African American children. Reduced production of FLG2 protein in atopic dermatitis skin lesions appears to contribute to a breakdown of the skin's protective barrier. The two *FLG2* mutations identified in the study are rarely found in atopic dermatitis patients of European origin, suggesting that the genes that contribute to atopic dermatitis vary by ethnicity. This finding underscores the importance of conducting genetic studies in minority patients.[1251]

The NIAMS National Multicultural Outreach Initiative was created to address disparities in minority populations' access to health information about conditions of the bones, joints, muscles, and skin.[1252] The initiative's flagship publication was a set of health planners culturally tailored for five different groups: African Americans; Hispanics/Latinos (bilingual); Asian Americans; American Indians or Alaska Natives; and Native Hawaiians or other Pacific Islanders. The health planners directed people to additional resources online. The information provided in the health planners and a quarterly electronic newsletter was curated from NIAMS, NIH, and other Federal agencies.[1253]

Mental Health

Mental health refers to social, emotional, and psychological well-being. People often develop mental health problems due to biological factors, life experiences, and family history of mental health problems.[1254] Mental health conditions are frequently unaddressed in minority groups, creating notable mental health disparities that affect people differently based on race and ethnicity, SES, and geographic location. Compared with the majority population, members of minority groups in the U.S. have lower

[1249] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-15-006.html.
[1250] Kranz AM, et al. *Pediatrics* 2015;136(1):107-14. PMID: 26122805.
[1251] Margolis DJ, et al. *J Allergy Clin Immunol* 2014;133(3):784-9. PMID: 24184149.
[1252] https://www.niams.nih.gov/community-outreach-initiative.
[1253] http://www.niams.nih.gov/News_and_Events/.
[1254] https://www.mentalhealth.gov/basics/what-is-mental-health/index.html.

mental health status, yet they are less likely to have access to quality mental health services, less likely to use community mental health services, and more likely to suffer from mental illness.[1255]

Mental health disparities represent a significant public health burden in the lesbian, gay, and bisexual communities. Bisexual women tend to fare the worst on a majority of health outcomes, with the most consistent and pronounced disparities in mental health. Exposure to microaggressions, daily stressors associated with minority status, may be more common among bisexual women and may explain health disparities among this group. In 2015, NIMHD began funding a project that uses e-diaries to examine the potential impact of microaggressions among bisexual women and gain a better understanding of microaggressions' role in mental health disparities.[1256]

Aging

In a study of 92 African American men ages 30–50, those who demonstrated a stronger implicit anti-Black bias and reported higher levels of racial discrimination had the shortest leukocyte telomere length (LTL). Telomere length is an indicator of biological aging, and shorter LTL is associated with earlier mortality. Shorter LTL has also been tied to many age-related health issues, such as heart disease, diabetes, dementia, Alzheimer's disease, and arthritis. This finding demonstrates a possible biological mechanism through which psychosocial factors may affect aging at the most basic molecular and cellular levels.[1257]

Technology Development

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, 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, ranging from basic early-stage research (e.g., microscopy and cellular analysis tools) to preclinical technologies (e.g., tissue chips, 3D scaffolds), as well

[1255] https://www.nimh.nih.gov/about/organization/gmh/minority-health-and-mental-health-disparities-program.shtml.
[1256] https://projectreporter.nih.gov/project_info_description.cfm?aid=8873307&icde=35334132.
[1257] Chae DH, et al. *Am J Prev Med* 2014;46(2):103-11. PMID: 24439343.

as postclinical, POC, and wearable sensor technologies that facilitate access to and provide better patient care. These innovations have not only provided unprecedented insights into complex biological processes but have also generated new methodologies that have transformed many fields of study. For example, NIH funding for biotechnology was $5,889 million in FY 2014 and $6,019 million in FY 2015; for bioengineering, it was $3,329 million in FY 2014 and $3,540 million in FY 2015.[1258] 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.

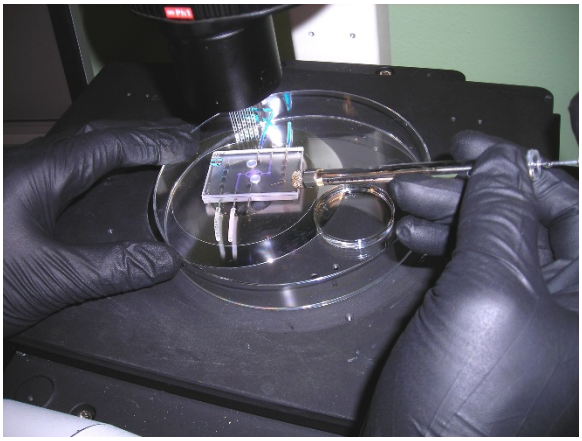

Figure 55. An NIH-funded tissue chip researcher works with a kidney-on-a-chip. Credit: University of Washington, Seattle.

Imaging and Microscopy

Microscopy, which involves the use of microscopes to view samples and objects that cannot be seen with the naked eye, allows us to see objects in varying levels of detail, ranging from tissues, to cells, organelles, and single molecules. Regardless of the imaging modality, NIH has consistently supported technological advancements of microscopy approaches that can better visualize, monitor, diagnose, and treat disease. In FY 2014, NIGMS started a new initiative to support imaging at a molecular level by establishing the Regional Consortia for High Resolution Cryoelectron Microscopy. Cryoelectron microscopy uses electron microscopy to image frozen-hydrated specimens at cryogenic temperatures. This technique allows scientists to study extremely fine cellular structures, viruses, and protein complexes at molecular resolution, providing greater detail than possible by other imaging techniques; unsurprisingly, it has transformed drug design. The NIGMS program, with the first awards made early in FY 2015, provides access to the state-of-the-art cryoelectron microscopy technology to a broad range of investigators.[1259] But since many research institutions do not have access to state-of-the-art microscopes, other techniques to gain better insights into biological processes were developed. For example, the Common Fund's NIH Director's Pioneer and Transformative Research Award supported the development of a paradigm-changing technique called expansion microscopy to greatly enhance the

[1258] https://report.nih.gov/categorical_spending.aspx.
[1259] http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-16-001.htm.

imaging of tiny cellular structures without the need for costly specialized equipment.[1260,1261] Expansion microscopy uses a material commonly found in diapers to hold proteins in place while expanding in the presence of water, resulting in minimal distortion of the tissue structure. Tissues can be expanded about four and a half times their normal size, enabling visualization of tiny cellular structures and proteins through ordinary microscopes.

Often, the limitation lies not in the spatial resolution of microscopes but rather in researchers' capability to process the images they have acquired. With that in mind, new open-source software was developed to help track the embryonic development and movement of neuronal cells throughout the body of the worm. A collaborative team led by NIBIB researchers developed new microscopes that improve the speed and resolution at which worm embryonic development could be imaged without damage from too much light exposure, while at the same time offering the resolution needed to clearly see individual cells.[1262,1263] Users of this software can also mark cells or structures that they want the program to track, allowing them to follow the position of a cell as it moves and grows in the developing worm embryo. This feature could help scientists understand how certain cells develop into neurons, as opposed to other types of cells, and what factors influence the development of the brain and neuronal structure.

These technical advancements can have wide-ranging impacts, including application in noninvasive imaging techniques to improve the health outcomes of patients. Technological advances moving at an unprecedented pace are beginning to make this possible. For example, as a part of its Audacious Goals Initiative, a 15-year initiative to restore vision by regenerating neurons and their connections in the retina and optic nerve, NEI funded five new projects that will develop new technology to noninvasively image cells of the back of the eye in unprecedented detail. The collaborative projects build on Adaptive Optics, a paradigm-shifting microscope technology that uses sensors and deformable mirrors to correct for the blur caused in the front of the eye.[1264] With this technology, it is now possible to successfully image a single photoreceptor cell and track that same cell in subsequent patient visits. This powerful tool allows clinicians to noninvasively monitor the degeneration of the cell and, conversely, to visualize its replacement by healthy stem cells. Building on Adaptive Optics and integrating it with complementary technologies will provide unprecedented access to retinal neurons and will pave the way for testing of new therapies. Similarly, NIDCR funded the development of videoscope-assisted minimally invasive periodontal surgery (V-MIS), which uses a very small digital camera to allow for easy visualization and magnification of the surgical site in the mouth. This invention shows promising results in preliminary testing and would be an improvement over a surgical microscope, allowing for minimally invasive gum surgery.[1265]

When the treatment requires invasive strategies, on the other hand, NIH has pioneered and funded research that develops more effective and targeted techniques. For example, a multidisciplinary team of

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[1260] Chen R, et al. *Science* 2015;347(6221):543-8. PMID: 25592419.
[1261] https://www.nih.gov/news-events/news-releases/diaper-compound-may-expand-power-microscopes.
[1262] Christensen RP, et al. *Elife* 2015;4-e10070. PMID: 26633880.
[1263] https://www.nibib.nih.gov/news-events/newsroom/how-developing-brain-assembled.
[1264] https://nei.nih.gov/news/pressreleases/neural_activity_retina.
[1265] Harrel SK, et al. *J Clin Periodontol* 2014;41(9):900-7. PMID: 25039580.

interventional radiologists, urologists, and molecular imaging programmers from NCI developed a novel paradigm of using MRI images to guide the placement of biopsy needles in the prostate without requiring the physical presence of the MRI scanner itself during the procedure.[1266] The MRI–ultrasound fusion detected more of the higher-grade prostate cancers and fewer of the low-grade cancers that could be a source of overtreatment. This technology could provide a smart targeted "man-o-gram" option for patients who otherwise would have undergone random, totally blinded biopsy, which has long been the standard technique. Similarly, NIBIB funded research that developed a fluorescence technology that makes tumors and nerves glow, to show a person's nerve course within the body and provide clearer margins on tumors.[1267,1268] This is especially important because nerves and vessels vary from person to person, and in surgery, a cookie-cutter approach, especially in relation to tumors that may be blocking a nerve, can lead to nerve damage and prevent surgeons from removing as much of the tumor as possible.

Cellular Function

A single cell can undergo many changes over its lifetime, including growth, division, movement, signal transduction, and alteration of gene expression. Changes in phenotypic markers and functional behaviors of cells are both of great interest, because they provide information and elucidate mechanisms of cellular response to different signals or environments. Being able to observe and track these changes can help researchers understand how different populations of cells respond and will ultimately help clinicians choose the most appropriate treatments.

The Common Fund's Single Cell Analysis program[1269] supported the development of inDrops, a new technology that quickly and easily gives each cell within a biological sample a unique genetic barcode, enabling researchers to determine the gene expression patterns of individual cells.[1270] Traditional approaches to analyzing samples rely on examining all the cells as a group, under the assumption that all cells behave the same. However, understanding biological properties of individual cells is important because growing evidence suggests that cells can differ dramatically, with important consequences for the health and function of the entire population. Using this approach, researchers will be able to identify new cell types, determine how cells within a sample vary in function, and identify which cells may be affected by or contribute to disease.

In 2014, the Single Cell Analysis Program launched the Follow that Cell Challenge to stimulate the development of new tools and methods that will enable researchers to predict the behavior and function of a single cell in complex tissue over time.[1271] This could help reveal valuable information, such as how cells transition from health to disease, or identify changes that influence a cell's responsiveness to treatment. During the first phase of the Challenge, innovators across a wide range of fields were

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[1266] Siddiqui MM, et al. *JAMA* 2015;313(4):390-7. PMID: 25626035.
[1267] Orosco, RK, et al. *J Surg Oncol* 2016;113(2):138-43. PMID: 26799257.
[1268] Hussain, T, et al. *Head Neck* 2016;38(5):715-23. PMID: 25521629.
[1269] http://commonfund.nih.gov/Singlecell/index.
[1270] Klein AM, et al. *Cell* 2015;161(5):1187-1201. PMID: 26000487.
[1271] https://www.nibib.nih.gov/news-events/newsroom/seeking-single-cells%E2%80%99-secrets.

encouraged to propose theoretical solutions for tracking and analyzing the behavior and function of individual cells over a period of minutes, hours, and even days. Sixteen projects were selected to advance to the second phase, which requires innovators to generate proof-of-concept data.[1272]

At a cellular level, the nucleus contains the genetic blueprint that encodes all the genes that an organism uses to carry out cellular functions. But this genetic material is not randomly organized. Although scientist know that the spatial configuration of DNA and DNA-associated proteins influences which genes are expressed how this happens is unknown. Researchers are just beginning to understand how the spatial configuration of genetic material influences gene expression and cellular function and how this changes during normal development and in disease. Launched in 2015, the Common Fund's 4D Nucleome program uses cutting-edge technologies and supports a diverse interdisciplinary consortium of investigators to transform the way we understand nuclear architecture and gene regulation.[1273] These geneticists, molecular biologists, mathematicians, biophysicists, and other experts are working together to unlock the mysteries of the nucleome and how its genetic code is organized and used. The goal of the 4D Nucleome program is to understand how changes in nuclear organization affect normal development as well as disease states.

A specific example where changes in gene expression have a direct impact on potential therapeutics is iPSCs, the use of which has been mentioned in several sections throughout this chapter. iPSCs show great potential as disease models and therapeutic agents, but a poor understanding of the reprogramming process may limit their usefulness. Technical innovations in stem cell biology provide new opportunities for scientific progress with pluripotent stem cells obtained from sources other than human embryos. In FY 2014 and FY 2015, NIGMS 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. NIGMS has entered into a $14 million, five-year cooperative agreement to continue operating the NIGMS Human Genetic Cell Repository, which includes many iPSC lines carrying disease gene mutations.[1274]

Although understanding how cellular function changes over time is important in identifying therapeutic targets, NIH's central goal is to prevent disease, if possible. Prion diseases pose a significant challenge: They are incurable, fatal, transmissible neurodegenerative disorders that go undetected in the brain for several years. The diseases originate when normally harmless prion proteins become abnormal (for reasons not yet fully understood) and gather in clusters. Until now, diagnosis required testing brain tissue obtained after death or by biopsy. Creutzfeldt-Jakob disease (CJD) is an invariably fatal human prion disease. Early and accurate diagnosis is important because prions are transmissible and unusually resistant to decontamination. Researchers in the NIAID IRP have now developed an improved assay, called real-time quaking-induced conversion (RT-QuIC), that uses cerebrospinal fluid rather than brain tissue to detect prions and that detects prions in 4–14 hours, with improved analytical sensitivity.[1275]

[1272] https://www.nibib.nih.gov/news-events/newsroom/nih-announces-follow-cell-challenge-finalists.
[1273] http://commonfund.nih.gov/4Dnucleome.
[1274] https://www.nigms.nih.gov/News/results/Pages/20150316.aspx.
[1275] Orrú, CD, et al. *MBio* 2015;6(1):pii-e02451-14. PMID: 25604790.

The new test should allow for much faster, more accurate, and practical testing for CJD, helping healthcare workers reduce transmission of the deadly prions. NIAID researchers also found that the prion protein is generated outside of blood vessels in the brain, where a drug treatment could potentially be targeted to prevent this disease.[1276]

Tissue Chips

Researchers spend a lot of time and money developing new drugs, yet 30 percent of candidates entering human clinical trials are found to be toxic—something that is often missed in preclinical studies in mice or other models—so there is a great need to develop technologies that better predict which drugs will be safe in humans. Tissue chips are engineered microsystems that are lined with living cells and contain features designed to replicate the complex biological functions of a specific human organ. This technology holds the promise of providing a model system far more analogous to the human body than any previous system. Once these models are developed and integrated, researchers can use them to more quickly and effectively predict whether a candidate drug, vaccine, or biologic agent is safe in humans.

To address this need, the Common Fund and more than 15 NIH ICs, led by NCATS, established the Tissue Chip for Drug Screening program in collaboration with DARPA and FDA. The aim is to develop microfabricated chips—called tissue chips or organs-on-chips—capable of maintaining living human cells and tissues that are organized to model intact human organ systems, eventually creating an integrated human body-on-a-chip.

Researchers within the Tissue Chip for Drug Screening Program, part of the Common Fund's Regulatory Science program,[1277] have developed a 3D organoid with many features of the human brain.[1278,1279] This neuronal tissue chip, developed in a lab dish, contains neurons, support cells, blood vessels, and immune cells, and it can be used to predict toxicity of drugs and other chemicals.[1280] When the brain organoid is exposed to compounds, a readout of the genetic activity can be decoded to determine whether the compound is likely to be toxic to a real human brain.

Tissue chips can be made for a variety of organs, including the heart. Barth syndrome, a rare genetic condition that occurs almost exclusively in men, weakens the muscles and enlarges the heart. In 2014, NCATS-funded researchers developed a Barth syndrome tissue chip of heart muscle cells, enabling the team to find the mechanism of the disease and led them to a potential treatment.[1281] Then in 2015, an NIH-funded team of scientists placed undifferentiated iPSCs onto a specifically engineered tissue culture dish etched with tiny circles that kept cells clustered together and forming a ball-like, 3D structure.[1282]

[1276] Chesebro B, et al. *MBio* 2015;6(5):e01419-15. PMID: 26396245.
[1277] https://commonfund.nih.gov/regulatoryscience.
[1278] Schwartz MP, et al. *Proc Natl Acad Sci USA* 2015; 6;112(40):12516-21. PMID: 26392547.
[1279] https://directorsblog.nih.gov/2015/09/29/if-i-only-had-a-brain-tissue-chips-predict-neurotoxicity/.
[1280] https://ncats.nih.gov/tissuechip.
[1281] https://ncats.nih.gov/tissuechip/chip/disease#barth.
[1282] Ma Z, et al. *Nat Commun* 2015;6:7413. PMID: 26172574.

These ball-like cardiac cells not only organized themselves into a tiny human heart chamber, but they also started to pulse and beat.[1283]

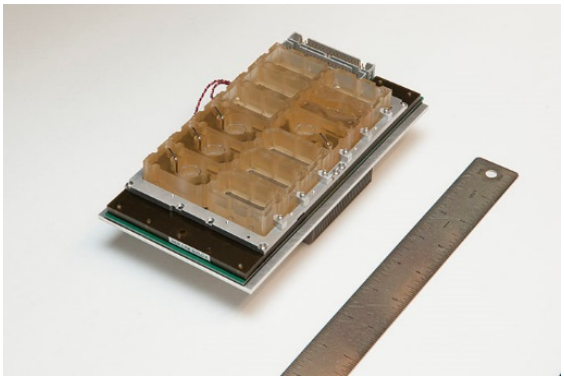

Figure 56. EVATAR™, the female reproductive tract and liver tissue chip. Credit: Northwestern University.

Other applications of tissue chip technologies supported through NCATS' tissue chip program include the development of EVATAR™—a miniature working 3D representation of the female reproductive tract, along with the liver.[1284] Since 2012, the EVATAR™ group has been refining the individual organ components and building the integrated 3D platform. The components of this model communicate through secreted substances, including hormones, to mimic how they work together in a woman's body in processes such as the 28-day reproductive cycle. When coupled with other tissue chips, EVATAR™ will be an invaluable tool in optimizing drugs and therapies for women.

3D Scaffold

In the field of tissue engineering, 3D scaffolds are often used for drug delivery, material studies, and investigation of cell behaviors. The development of scaffolds for regenerative medicine applications is an important area of investigation, because such scaffolds not only serve as building blocks for the formation of new tissues but also guide tissue regeneration through delivery of active biomolecules and drugs to specific sites in the body. Tissue engineers develop 3D scaffolds to mimic the in vivo microenvironment where the cells interact and behave in response to the mechanical cues obtained from the local environment.

In 2014, NHLBI created a program to support multidisciplinary small business teams in the development of complex, 3D engineering systems for growing heart, lung, or bone marrow tissue.[1285] This program has the potential to drive progress in the development of tissues that could be used to repair damaged organs. While other researchers have succeeded in using a highly specialized 3D printing system to craft joints, bones, and splints[1286] and have made miniature organs by layering human cells,[1287] one group of

[1283] https://directorsblog.nih.gov/2015/07/21/bioengineering-big-potential-in-tiny-3d-heart-chambers/.
[1284] https://ncats.nih.gov/pubs/features/evatar.
[1285] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-017.html.
[1286] Ledford, H. *Nature* 2015;520(7547):273. PMID: 25877182.
[1287] Murphy, SV, et al. *Nat Biotechnol* 2014;32(8):773-85. PMID: 25093879.

researchers was able to use a gel-in-gel technique to prevent 3D printed scaffolds from collapsing under their own weight.[1288] This innovative approach was able to generate a variety of scaffolds that could be seeded with live cells and was supported by the Common Fund's NIH Director's New Innovator Award.[1289] Similarly, NIDCR-supported investigators developed a new paradigm using a scaffold that can be injected into the body with a simple syringe.[1290] These novel scaffolds can bind both water-soluble and water-insoluble drugs and deliver them to tissues in a controlled manner. Because of these unique properties, these scaffolds have the potential to provide a versatile and highly adjustable delivery platform for a broad range of therapeutic compounds.

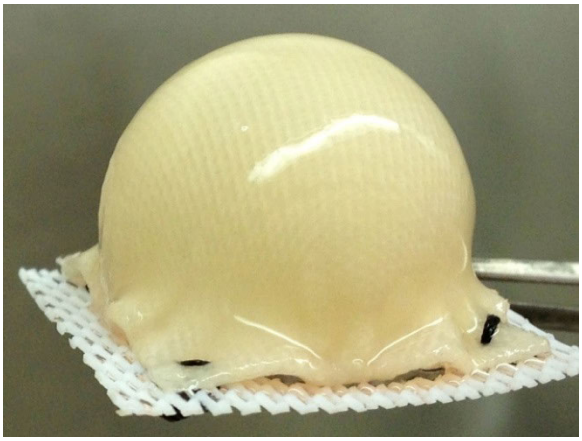

Figure 57. 3D scaffold engineered to guide stem cells into cartilage-producing cells. Credit: Guilak Lab, Washington University.

Wearable Sensors

NIH-supported scientists have been developing wearable sensors, smart electronic devices that can be worn as an accessory and can monitor a person's heart rate, skin temperature, and other health variables to study people at an individual level. In 2015, NIAAA issued the *Wearable Alcohol Biosensor Challenge* to stimulate the design of a discreet, noninvasive wearable device capable of measuring blood alcohol levels in near real-time.[1291] An improved alcohol biosensor could be a valuable resource for the alcohol research community, reducing reliance on participant self-report in scientific studies. The winning prototype of the Challenge was the BACtrack Skyn, a device that is worn on the wrist and offers continuous and noninvasive monitoring of a user's blood alcohol level, using fuel cell technology similar to devices used by law enforcement in roadside alcohol testing.[1292] BACtrack, a company known for designing and selling portable breath alcohol testers for consumer and professional use, submitted the winning prototype and received the $200,000 first prize.

[1288] Hinton, TJ, et al. *Sci Adv* 2015;1(9):e1500758. PIMD: 26601312.
[1289] https://directorsblog.nih.gov/2015/11/03/building-a-better-scaffold-for-3d-bioprinting/.
[1290] Appel, EA, et al. *Nat Comm* 2015; 6:6295. PMID: 25695516.
[1291] https://www.challenge.gov/challenge/a-wearable-alcohol-biosensor/.
[1292] https://www.niaaa.nih.gov/news-events/news-releases/niaaa-selects-winners-its-wearable-alcohol-biosensor-challenge.

Within the same research vein, a study using modified silicone wristbands allowed NIEHS-funded scientists to measure what the silicone had absorbed: 49 different substances, including PAHs, some of which have been linked to cancer, and compounds from pesticides and consumer products (the wristband can actually screen for more than 1,000 chemicals that may accumulate.[1293] Such wearable technologies are interwoven into daily life and different health parameters and will eventually allow doctors to understand different ailments and provide better care for individuals.

Mobile Health and Point-of-Care Technology

The U.S. has the highest annual per capita health expenditure of any developed country, yet our population still faces significant health challenges. One of the proposed research funding changes is to emphasize patient-centered approaches and coordinate care teams that promote wellness and effective disease management at a reduced cost by responding to the needs of an increasingly unhealthy population of individuals with multiple chronic conditions. These changes require the development of inexpensive and easy-to-use medical devices and information-sharing tools that provide timely health status information at the point of care. NIBIB has long supported POC development through the Point-of-Care Technology Resource Network.[1294] For example, NHLBI funds two initiatives to support research using advanced technologies (such as biochips and mobile technologies) to develop novel POC devices that could guide diagnostic and therapeutic efforts for heart, lung, blood, and sleep disorders.[1295,1296]

POC technologies have become increasingly valuable for improving or enhancing the diagnosis of conditions such as congestive heart failure and asthma. The kinds of tools that might result from these initiatives include breath test devices to monitor or diagnose heart, lung, or blood disorders, and a device to monitor vulnerable patients after a heart or lung transplant.

Similarly, in 2015, NIDCR launched new initiatives to encourage research to develop the next-generation of rapid tests and point-of-care diagnostic devices.[1297,1298] These tools use oral biospecimens, such as saliva or cells, to detect oral pathogens and biomarkers associated with oral diseases and to facilitate screening, monitoring, and diagnosis. The ultimate goal of these studies is to produce highly reliable, reproducible, specific, and sensitive tools for early detection and diagnosis of oral diseases, including those associated with HIV/AIDS. These methods must demonstrate superior technical performance compared with current technologies, while not increasing costs and minimizing the invasiveness of specimen collection from patients.

In collaboration with the NINDS Human Motor Control Section, NLM developed a mobile health application for people with PD to help patients keep detailed records of their daily health. The tablet application enables patients to track and record information about their symptoms and management of

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[1293] O'Connell SG, et al. *Environ Sci Technol* 2014;48(6):3327-3335. PMID: 24548134.
[1294] https://www.nibib.nih.gov/research-funding/point-care-technologies-research-network.
[1295] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-017.html.
[1296] http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-011.html.
[1297] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-15-001.html.
[1298] https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-15-002.html.

them, including dyskinesia, tremors, mood, falling, speech, and medications, between doctor visits.[1299] Such tracking can provide the treating neurologist with an objective account of a PD patient's health condition and allow the physician to tailor treatment for the patient and improve overall patient care. For example, to maximize patient quality of life, physicians can use these data from the PD Diary to tailor a PD patient's L-DOPA dosage and frequency to maximize on times with no or non-limiting dyskinesia. During FY 2014 and FY 2015, NLM and NINDS observed and interviewed 22 PD patients to help design this mobile app, which is expected to begin clinical trials in FY 2016.

Mobile technology is particularly well suited for LMICs. FIC's Mobile Health Program aims to contribute to the evidence base for the use of mobile technology to improve clinical outcomes and public health while building research capacity in LMICs and establishing research networks. For example, one group developed a smartphone-powered malaria screening device that uses a technique called magnetic levitation, which analyzes red blood cells and can also detect sickle cell disease. New research is needed to develop mobile technologies tailored to LMIC settings, assess the technologies' impact on health, and determine how they can be effectively scaled up in diverse, low-resource settings. [1300]

NLM intramural scientists are actively investigating the use of mobile technology to diagnose TB and malaria in lo-resource settings. For malaria detection, NLM developed image analysis and machine learning algorithms to discriminate between parasite-infected and uninfected red blood cells and to report the parasite count (indicating malarial infection) per microliter of blood.[1301] Scientists have developed an app based on these algorithms and ported it to a smartphone.[1302] The app, which attaches a smartphone to the eyepiece of a conventional microscope with a low-cost adapter, is in field tests in Bangladesh. Collaborators include the Mahidol-Oxford Tropical Medicine Research Unit in Thailand, Chittagong Medical College Hospital in Bangladesh, and the University of Missouri in the U.S.

NLM also developed computer-aided pulmonary TB screening of chest X-rays. The project leverages NLM's in-house expertise in image processing and communication to produce digital chest radiographs at remote rural sites and automatically screen HIV-positive patients for evidence of TB and other important pathology; this is important because TB coinfection in HIV positive patients makes treatment of both infections more difficult. The software was developed to analyze chest X-ray images and automatically segment the lungs; detect and dismiss images of the ribs, heart, aorta, and other structures; and then detect texture features characteristic of pulmonary disease.[1303,1304,1305,1306,1307] During FY 2014 and FY 2015, NLM developed a robust portable chest X-ray screening system for TB,

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[1299] Kim, B, et al. *Neuroscience and Biomedical Engineering* 2015;3(1):40-48.
[1300] https://www.fic.nih.gov/programs/pages/mhealth.aspx.
[1301] Poostchi, M, et al. NIH-IEEE Strategic Conference on Healthcare Innovations and Point-of-Care Technologies for Precision Medicine 2015.
[1302] https://www.hhs.gov/idealab/projects-item/automated-cell-counting-for-malaria-detection/.
[1303] Santosh, KC, et al. *Int J Comput Assist Radiol Surg* 2016;11(9):1637-46. PMID: 26995600.
[1304] Karargyris, A, et al. *Int J Comput Assist Radiol Surg* 2016;11(1):99-106. PMID: 26092662.
[1305] Jaeger, S, et al. *Quant Imaging Med Surg* 2014;4(6):475-7. PMID: 25525580.
[1306] Candemir, S, et al. *IEEE Trans Med Imaging* 2014;33(2):577-90. PMID: 24239990.
[1307] https://lhncbc.nlm.nih.gov/publication/pub9126.

deploying it in rural Kenya in collaboration with the Academic Model Providing Access to Healthcare (AMPATH) and FY 2014 from HHS Ignite, a departmental initiative of the HHS Innovation Council.

NIAID supported the development of three POC diagnostics that were granted Emergency Use Authorization from FDA during the Ebola outbreak: the FilmArray Biothreat E-test from BioFire Defense LLC,[1308] and the Xpert Ebola Test from Cepheid,[1309] which detect viral nucleic acids; and the ReEBOV Antigen Rapid Test Kit from Corgenix, which detects the Ebola protein.[1310]

Research Resources and Infrastructure

NIH relies on key resources and infrastructure to support the conduct of biomedical research and enhance health. Databases and biorepositories enable access to a wide range of biological samples and data—by the researchers and, in some cases, the public. Similarly, research centers and networks allow the sharing of information and resources focused on a specific disease or research community to educate, build knowledge, or collaborate. Researchers utilize the latest technologies in data science and computational science to develop new tools and scientific applications to further enhance biomedical research. NIH also seeks collaborations and partnerships with other Federal agencies, industry, and academia to maximize and diversify knowledge and expertise to treat, cure, and prevent disease. In FY 2014 and FY 2015, NIH ICs conducted numerous activities related to maintaining and enhancing the research infrastructure and available research resources within the NIH IRP, as well as the extramural research community. The follow subsections highlight several exciting activities relating to this reporting period; additional updates on resources and infrastructure are included throughout Chapter 3.

Databases and Data Sharing

NIH supports the concept of data sharing and believes that it is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. NIH endorses the sharing of final research data to serve these and other important scientific goals, operating several databases that make data available to both the public and approved investigators. NLM houses many of NIH's databases, such as PubMed and ClinicalTrials.gov; several other ICs maintain their own databases, such as Trans-Omics for Precision Medicine (TOPMed) and the ENCyclopedia Of DNA Elements (ENCODE).

The range of information that NLM organizes and disseminates includes published and unpublished research results; decision support resources; health information for the public; and genetic, genomic, and biochemical data. NLM's numerous information systems play a key role in catalyzing and supporting

[1308] http://www.biofiredx.com/wp-content/uploads/2016/03/PRESS_RELEASE-BioFire_Defense_receives_emergency_use_authorization_of_FilmArray_Ebola_Tests_10252014.pdf.
[1309] http://ir.cepheid.com/releasedetail.cfm?releaseid=903155.
[1310] https://www.corgenix.com/news-releases/corgenix-receives-fda-authorization-and-who-listing-for-emergency-use-of-ebola-rapid-diagnostic-test/.

the translation of basic science into new treatments, new products, improved practice, and useful decision support for health professionals and patients.

NLM's PubMed[1311] provides access to approximately 26 million authoritative biomedical journal references and is accessed each day by millions of people, ranging from scientists performing research, health professionals looking for the latest information on medical conditions to the general public seeking information on health problems. During FY 2014 and FY2015, NLM indexed more than 1.5 million new journal articles for inclusion in PubMed. In FY 2014, NLM implemented PubMed Commons,[1312] which allows PubMed authors to provide substantive, signed public comments on the methods and results of other articles in PubMed.

During FY 2014 and FY 2015, PubMed Central (PMC),[1313] which provides free permanent electronic access to the full text of biomedical and life sciences journal articles and serves more than 1 million users each day, added more than 600,000 articles and offered access to more than 3.9 million articles from journals that agreed to share their content as well as to those manuscripts submitted as a result of the mandatory NIH Public Access Policy. PMC continued to expand as a result of the White House Office of Science and Technology Policy's 2013 directive that Federal agencies with more than $100 million in R&D expenditures make their federally funded research freely available to the public. Recognizing PMC's success, in 2015, many Federal agencies, including CDC, FDA, VA, NASA and the National Institute of Standards and Technology (NIST), decided to use PMC to manage their requirements under the directive.

In conjunction with multiple NIH ICs, NLM issued 22 additional Administrative Supplements for Information Services in NIH-funded Research Projects to continue to evaluate the use of librarians and other information specialists in improving data collection, curation, management, and sharing in NIH-funded research. NLM also conducted a study to inform efforts to improve the discoverability of and access to biomedical datasets by providing a preliminary estimate of the number and type of datasets generated annually by research funded by NIH.[1314]

In FY 2014 and FY 2015, nearly 5,500 printed historic books, more than 4,000 historic images, and nearly 900 manuscripts were digitized and added to NLM's Digital Collections,[1315] a free online archive of biomedical books and videos. These collections are heavily used by scholars, the media, and the general public. In partnership with the Wellcome Library, one of the world's leading libraries of medical history, NLM is coordinating a three-year project to digitize historically significant journals charting the development of modern medicine over the last 150 years. Digitization started in late 2014, and content is freely available via PMC and its European counterpart, Europe PMC.

[1311] http://www.ncbi.nlm.nih.gov/pubmed/.
[1312] http://www.ncbi.nlm.nih.gov/pubmedcommons/.
[1313] http://www.ncbi.nlm.nih.gov/pmc/.
[1314] Read KB, et al. *PLoS ONE* 2015;10(7). PMID: 26207759.
[1315] http://collections.nlm.nih.gov/.

In FY 2015, the NIH ODP developed a new Web portal, Resources for Researchers, to help prevention researchers access information useful for designing and conducting their studies. This portal combines prevention-related information across various NIH websites with newly created tools and materials in one online repository specifically tailored to the needs of the prevention research community.[1316]

As part of its work to improve access to health services research (HSR) and public health information, NLM produces web portals aimed at health services researchers. HSR Information Central[1317] and Partners in Information Access for the Public Health Workforce[1318] are two such NIH-funded portals, the latter developed in conjunction with other agencies and organizations for the public health community. These portals feature access to a wide variety of information and specialized resources, including Health Services Research Projects in Progress (HSRProj),[1319] which contains HSR projects funded by more than 350 governmental and private funders. In FY 2014 and FY 2015, HSRProj added more than 3,000 new projects, growing the database to more than 29,000 projects. In 2015, PCORI designated HSRProj as one of the three repositories that its grantees must use to satisfy requirements for project registration and submission of project results in ClinicalTrials.gov. Another notable resource, Health Services and Sciences Research Resources (HSRR),[1320] is a searchable catalog of research datasets, instruments, and software relevant to HSR, behavioral and social sciences, and public health. The database hosted a total of 1,466 records at the end of FY 2015.

NLM develops, funds, and disseminates the clinical terminologies designated as U.S. standards for use in electronic health records and health information exchange; NLM also produces tools that help EHR developers and users implement these standards and makes them available in multiple formats, including via application programming interfaces (APIs). NLM's technical and financial support enables clinical terminology standards to be updated regularly to reflect new drugs, tests, devices, and changes in medical knowledge and health practice, as well as allowing them to be used free of charge in U.S. health care, public health, biomedical research, and product development.

In cooperation with FDA, NLM launched AccessGUDID in early 2015 to enable search and retrieval of the more than 200,000 records in FDA's Global Unique Device Identifier Database (GUDID), to which information is submitted by medical device manufacturers. NLM also established a Web API service that allows computers to retrieve medical device information by unique device identifier, so that EHR systems can retrieve implantable device information for incorporation in patient records.

NLM expanded and enhanced the APIs to the RxNorm[1321] clinical drug terminology standard and related prescription drug information sources, resulting in 1 billion API queries in 2015. NLM also added a new feature to compute the similarity between two classes of medications and used these tools and large

[1316] https://prevention.nih.gov/resources-for-researchers.
[1317] https://www.nlm.nih.gov/hsrinfo/.
[1318] https://phpartners.org/.
[1319] http://www.nlm.nih.gov/hsrproj/.
[1320] https://wwwcf.nlm.nih.gov/hsrr_search/.
[1321] https://www.nlm.nih.gov/research/umls/rxnorm/.

drug prescriptions databases to study the effects of prescription drugs with fetal risk on pregnant women.[1322,1323]

The Computational Photography Project for Pill Identification[1324] used a public challenge mechanism to support development of algorithms that can correctly identify pills from pictures taken on smartphones. Computer vision research in text- and image-based search mechanisms is being conducted in order to identify pills, using photos matched to images in an authoritative, comprehensive, public digital image inventory of the nation's commercial solid-dose prescription medications. The database will also help the pharmaceutical industry provide pill images in public information.

Dietary supplements, used regularly by about half of U.S. adults, can add significant amounts of nutrients and other ingredients to the diet, resulting in various health risks and benefits. As of the end of FY 2015, the Dietary Supplement Label Database (DSLD),[1325] managed by NLM and NIH's ODS, contains information from the labels of approximately 50,000 dietary supplement products available in the U.S. marketplace. Made available to the public in June 2013, this free resource is expected to grow to include most of the different dietary supplements sold.

In 2015, NIDDK, in conjunction with NLM, supported the expansion of the LiverTox website, which 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 help health care providers diagnose, and investigators study, liver injury due to drugs and herbs/supplements.[1326]

The PubChem database[1327] houses the voluminous data on molecular structures and chemical functions submitted by more than 380 organizations. It provides information about the biological activity of small molecules, organized as three linked databases and a chemical structure similarity search tool. During 2014 and 2015, NLM added 13 million distinct compounds and 300,000 bioassays, so that PubChem contained data on more than 60 million distinct compounds and results from more than 1.1 million bioassays. The data in PubChem is also linked to multiple genomic databases and the biomedical literature.

GenBank,[1328] the NIH genetic sequence database operated by NLM, is an annotated collection of all publically available DNA sequences. It is designed to provide access to the most up-to-date and comprehensive DNA sequence information; as of the end of 2015, it contained approximately 185 million sequences from more than 365,000 different species. In FY 2015, 10 million new sequences were added, including approximately 55,000 new species represented in the database.

[1322] Peters LB, et al. *AMIA Ann Symp Proc* 2015;1034-1041. PMID: 26958241.
[1323] Peters LB, et al. *J Biomed Semantics* 2015;6:19. PMID: 25964850.
[1324] https://lhncbc.nlm.nih.gov/project/c3pi-computational-photography-project-pill-identification.
[1325] http://www.dsld.nlm.nih.gov/dsld/.
[1326] http://livertox.nih.gov/.
[1327] https://pubchem.ncbi.nlm.nih.gov/.
[1328] https://www.ncbi.nlm.nih.gov/genbank/.

NIH's Database of Genotypes and Phenotypes,[1329]developed and operated by NLM, houses data from a number of genome-wide association studies, which explore the connection between common variants of specific genes (genotype information) and observable diseases or conditions (phenotype information, such as diabetes, high blood pressure, or obesity). NIH encourages its grantees to submit their GWAS data, as well as other studies, to dbGaP and has established procedures for making the data available to other researchers to speed up disease gene discovery, while at the same time protecting the privacy of research subjects in genomics studies. In 2015, dbGaP grew by more than 20 percent to contain more than 600 studies involving more than 1 million people.

NLM's Genetic Testing Registry (GTR)[1330] provides a central location for voluntary submission of genetic test information by health care providers. Each record includes the test's purpose, methodology, and validity; evidence of the test's usefulness; and laboratory contacts and credentials. The overarching goal is to advance the public health and research into the genetic bases of health and disease. In FY 2014, the number of genetic tests listed doubled to 32,000.

The ENCODE Project,[1331] an ambitious research program run by NHGRI, is cataloging the functional regions of the human genome that regulate where and when individual genes or groups of genes are turned on or off. In FY 2014 and FY 2015, ENCODE significantly expanded the number of functional DNA elements studied and scaled up the analysis of RNA-binding proteins and RNA elements. This resource is already being used by researchers across the biomedical research enterprise to power tomorrow's breakthroughs, and scientists have used ENCODE data for important discoveries relevant to the study of Alzheimer's disease, diabetes, cancer, and cardiovascular disease.

As of FY 2015, he Common Fund's Epigenomics Program[1332] had generated and analyzed more than 100 reference human epigenomes, the largest collection to date, from a broad range of representative primary cells and tissues.[1333] Epigenomics is the study of the chemical modifications that sit "on top of" the DNA and affect gene expression without altering the underlying gene sequence. Researchers are beginning to understand the many consequences of these epigenomic modifications, and insights from these new analyses are revealing that different epigenomic states are associated with differences in age, sex, tissue type, and health/disease state. The wealth of reference genomes produced by the Epigenomics Program will significantly enhance research into the myriad epigenetic modifications that influence both normal development and a wide range of diseases.

NHLBI recently initiated the TOPMed[1334] program, which seeks to combine molecular, clinical, environmental, and other data from multiple populations into a single data resource. Researchers would then be able to pull relevant data on particular populations, such as a distinct ethnic group or patients from different ethnic groups who share a particular genetic sequence. Such studies could help reveal the

[1329] http://www.ncbi.nlm.nih.gov/gap.
[1330] https://www.ncbi.nlm.nih.gov/gtr/.
[1331] https://www.encodeproject.org/.
[1332] http://commonfund.nih.gov/epigenomics/index.
[1333] Roadmap Epigenomics Consortium, et al. *Nature* 2015;518(7539):317-30. PMID: 25693563.
[1334] http://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed.

combination of factors that contribute to unique susceptibilities and resilience to diseases in different groups.

Researchers supported by NIAID developed a database called ImmuNet[1335] that predicts genes and proteins in immunological diseases and processes, incorporating public high-throughput datasets. Utilization of this resource has led to the discovery of unique host–virus interactions and the prediction of disease-associated genes.[1336] ImmuNet and its associated mining tools are available to the public and should support the investigation of mechanisms of the human immune system and immunological diseases.

In FY 2014, a new initiative expanded the research focus of the NIDCR-supported FaceBase Consortium to include craniofacial anatomy beyond the midface (the middle of the face, including the nose and its associated bony structures). The consortium's goal is to foster cross-disciplinary research into craniofacial development and dysmorphologies and to make large datasets available to the wider research community.[1337] FaceBase is a major part of NIDCR's effort to enhance interdisciplinary collaboration, data sharing, and data science. To that end, the consortium's bioinformatics researchers and bench scientists are collaborating to develop strategies to make the data readily searchable by outside users of the website, using the FAIR (findable, accessible, interoperable, and reproducible) principles.

NIMH's first major effort to share clinical trial research data was established before many current data registries existed.[1338] The NIMH Limited Access Datasets (LAD) project, including data from 23 large, NIMH-supported clinical trials, sent out its 300th dataset in FY 2014. Advances in big data and informatics since the LAD project was established have created new means for encouraging widespread data sharing. NIMH developed a series of federated data repositories, collectively termed the NIMH Data Archive,[1339] which enable storage from data from a variety of studies to be stored; repositories include the National Database for Autism Research (NDAR),[1340] the National Database for Clinical Trials Related to Mental Illness (NDCT),[1341] the Research Domain Criteria Database (RDoCdb),[1342] and the Adolescent Brain Cognitive Development (ABCD) database.[1343]

NINDS and NIDA support the Neuroscience Information Framework (NIF), a dynamic inventory of Web-based neuroscience resources (data, materials, and tools), accessible to the public and provided in a framework that advances neuroscience research by enabling discovery and access to public research data and tools worldwide through an open-source, networked environment.[1344] NIF helped launch the

[1335] http://immunet.princeton.edu/.
[1336] Gorenshteyn D, et al. *Immunity* 2015;43(3):605-614. PMID: 26362267.
[1337] https://www.facebase.org/.
[1338] https://www.nimh.nih.gov/news/science-news/2015/pioneering-nimh-data-sharing.shtml.
[1339] http://data-archive.nimh.nih.gov/.
[1340] http://data-archive.nimh.nih.gov/#NDAR-anchor.
[1341] http://data-archive.nimh.nih.gov/#NDCT-anchor.
[1342] http://data-archive.nimh.nih.gov/#RDoCdb-anchor.
[1343] http://data-archive.nimh.nih.gov/#ABCD-anchor.
[1344] https://www.neuinfo.org/.

Resource Identification Initiative (RII) project[1345] in collaboration with FORCE11 (Future of Research Communications and e-Scholarships Community, a community seeking to modernize and enrich scholarly communication), leading to a new type of identifier that uniquely identifies key resources in the literature and already appears in more than 300 papers from 47 journals. NIF has been successful in raising over two-thirds of its operating costs through the development of SciCrunch, a unique platform for data science built from NIF technologies.[1346] In a cost-effective model for accessing resources, SciCrunch allows communities to use customizable templates and federated data sources to create portals that are immediately available to all the other SciCrunch communities.

NINDS has worked with disease-specific experts and other stakeholders as part of the Common Data Elements (CDE) program to develop standards to facilitate data collection, analysis, and sharing across the research community.[1347] To date, this effort has led to the development of a set of core and disease-specific data elements for numerous conditions, including three in FY 2014 and FY 2015: mitochondrial disease, facioscapulohumeral muscular dystrophy, and myotonic dystrophy. NLM launched the NIH CDE Repository[1348] to provide integrated access to NIH-supported CDEs and forms, as well as other HHS CDE initiatives. NLM provided tools that can be used to search, browse, compare, and create CDEs and forms, helping promote improved data quality and data reuse in clinical research and other contexts.

FITBIR Informatics System,[1349] funded by NINDS, NIH's Center for Information Technology, and DoD, was developed in FY 2014 and FY 2015 to share data across the entire TBI research field and to facilitate collaboration between laboratories, as well as interconnectivity with other informatics platforms. TBI investigators funded by NIH and DoD have contributed more than 200,000 patient clinical records from more than 4,500 patients to the FITBIR Informatics System.

Repositories and Biobanks

Biobanks and repositories are critical for conducting biomedical research, as they enable the collection, storage, preservation, and distribution of biospecimens such as blood, DNA, and tissue that researchers can use to study a diverse set of samples. NIH both maintains its own repositories and funds several repositories at academic institutions. A few examples are highlighted below; others appear throughout this report.

The Common Fund's GTEx[1350] program provides valuable insights into the mechanisms of gene regulation by studying human gene expression and regulation in tissues from healthy individuals; exploring disease-related perturbations in a variety of human diseases; and examining sexual dimorphisms in gene expression and regulation. GTEx resources include a database and tissue bank that researchers around the world can use. The genetic variation between individuals that underlies the

[1345] https://www.force11.org/group/resource-identification-initiative.
[1346] https://scicrunch.org/.
[1347] https://commondataelements.ninds.nih.gov/#page=Default.
[1348] https://www.nlm.nih.gov/cde/.
[1349] https://fitbir.nih.gov/.
[1350] https://commonfund.nih.gov/GTEx.

many differences in gene expression will be examined for correlation with differences in gene expression level to identify regions of the genome that influence whether and how much a gene is expressed. Identifying unique genomic variations associated with gene expression is expected to stimulate research toward understanding the genetic basis of complex diseases. In FY 2014 and FY 2015, two key manuscripts related to the GTEx biobank were published.[1351,1352] A two-day symposium, "The Genotype Tissue Expression (GTEx) Symposium: All Things Considered — Biospecimens, Omics Data, and Ethical Issues," was held in May 2015 at NIH and covered a broad range of topics that focus on the collection of normal biospecimens for GTEx.[1353]

Figure 58. Established in 1953, the Coriell Institute for Medical Research distributes cell lines and DNA samples to researchers around the world. Shown here are Coriell's cryogenic tanks filled with liquid nitrogen and millions of vials of frozen cells. Credit: Courtney Sill, Ph.D., Coriell Institute for Medical Research.

The NIGMS Human Genetic Cell Repository,[1354] established in 1972 and housed at the Coriell Institute for Medical Research, is a collection of well-characterized, high-quality human cells for use in biomedical research. Nearly 900 diseases and more than 40 population groups are currently represented in the repository, which also includes a collection of iPS cell lines that carry disease gene mutations or are normal controls. In FY 2014 and FY 2015, demand for cell and DNA samples from the repository remained high, with more than 5,000 cell and 34,000 DNA samples distributed per year.

The NINDS Human Genetics Resource Center formerly housed and distributed samples and clinical data from approximately 38,000 people with cerebrovascular disease, dystonia, epilepsy, frontotemporal degeneration, Huntington's disease, motor neuron disease, Parkinsonism, and Tourette syndrome, as well as neurological controls. Since its inception in 2002, the Center has distributed 32,951 samples and been cited by more than 350 publications. In 2015, the Center's collection was divided into two separate repositories: fibroblasts, iPSCs, and lymphoblastoid cell lines are now held by the NINDS Human Cell and

[1351] Carithers LJ, et al. *Biopreservation and Biobanking* 2015;13(5):311-319. PMID: 26484571.
[1352] GTEx Consortium. *Science* 2015;348(6235):648-660. PMID: 26484571.
[1353] https://meetings.nigms.nih.gov/Home/General/19217.
[1354] https://www.nigms.nih.gov/Research/SpecificAreas/HGCR/Pages/default.aspx.

Data Repository at Rutgers;[1355] samples of DNA, RNA, serum, cerebrospinal fluid (CSF), saliva, and urine are now held by BioSEND, the NINDS biomarker repository at Indiana University.[1356]

Research Centers and Networks

Research centers and networks support the collection, storage, and dissemination of scientific data accessed by the scientific community and the public for research and educational/informational purposes. NIH funds many such centers and networks, such as IRBrely or NCI's Biospecimen Research Network. Some key NIH center and network updates are presented below.

In FY 2014, NIAID initiated funding of Bioinformatics Resource Centers for Infectious Diseases (BRCs), which provide the scientific community with publicly accessible systems that store, update, integrate, and display genome sequence data and its annotation; functional genomics and other -omics data; and other associated information. Data cover a wide variety of human pathogens and vectors of human pathogens and related microbial species and strains, and users can query and analyze the data with user-friendly interfaces and computational analyses tools. BRCs have become the public repository of data generated by NIAID-supported genomics programs and other grants and contracts.

In FY 2014, NIAID also funded Genomics Centers for Infectious Diseases, a collaborative program that will use a combination of next-generation sequencing and related genomic technologies, bioinformatics capabilities, and computational analyses to understand infectious diseases, with a focus on the pathogen and its interaction with the host. The knowledge generated, including research data, analytical software tools, computational models, experimental protocols, and reagents, is expected to be widely disseminated to the scientific community through publicly accessible databases and reagent repositories.

To better inform consumers and their health care providers, NCCIH supports research on the biological mechanisms of the benefits and potential harmful effects of natural products, including their interactions with medications and potential liver toxicity. In FY 2015, NCCIH established a Center of Excellence for Natural Product-Drug Interaction Research.[1357] The new center is systematically examining ways to study natural product–drug interactions; developing standardized protocols to clarify which interactions have clinical impact; and disseminating the study findings and resources broadly. To support research innovation, NCCIH and ODS jointly funded two new Centers for Advancing Natural Products Innovation and Technology that will develop pioneering methods and techniques to catalyze new research approaches and technologies to make a significant impact on the chemical and biological investigation of natural products. Once developed, the centers will disseminate those resources to the larger research community.

[1355] https://grants.nih.gov/grants/guide/notice-files/NOT-NS-16-003.html.
[1356] https://grants.nih.gov/grants/guide/notice-files/NOT-NS-15-046.html.
[1357] https://nccih.nih.gov/research/blog/leadership-natural-product.

NIBIB participates in the Quantitative Imaging Biomarkers Alliance (QIBA),[1358] which brings together researchers, healthcare professionals, and industry stakeholders to advance quantitative imaging and the use of biomarkers in clinical trials and practice. QIBA currently has 12 biomarker committees and 15 task forces that are developing profiles and protocols for 16 quantitative imaging biomarkers. Dozens of articles have been published through this collaboration. Software, datasets, and physical and virtual phantoms for use in research and clinical practice are also available.

In 2015, the NCATS CTSA Program investigators created IRBrely,[1359] a national IRB reliance agreement that builds upon the expertise of existing regional IRB models. A pilot has been launched to test forms, workflows, and standard operating procedures related to IRBrely. In addition, CTSA researchers at University of Pittsburgh, UCSD, and UT Southwestern Medical Center are leading the CTSA Accrual to Clinical Trials (CTSA ACT)[1360] initiative to develop a nationwide network of sites that will share EHR data to identify and enroll participants who meet criteria for a given clinical study.

NCI completed the first phase of the Biospecimen Research Network (BRN),[1361] focused on the effects of biospecimen pre-analytical variation on molecular data, in FY 2014 and FY 2015. The BRN program's goal is to better understand the variability in research results that is introduced by different biospecimen collection, processing, and storage procedures, with the ultimate goal of increasing research reproducibility.

A highly successful translational research initiative led by NHGRI, the Electronic Medical Records and Genomics (eMERGE) Network[1362] has brought together researchers with expertise in genomics, statistics, bioethics, bioinformatics, and clinical medicine to develop, disseminate, and apply research approaches that combine genome sequence information with EHR systems. In FY 2015, a major new pharmacogenomic component of eMERGE studied the variation in 85 genes related to drug metabolism, feeding that information back to clinicians to aid in drug-prescribing decisions.

In FY 2014, NIGMS began an initiative to produce tools and technologies to unleash the chemical diversity of natural products encoded in fungi, plants, and bacteria for drug development. In FY 2015, NIGMS awarded and assembled the Genomes to Natural Products Network[1363] to provide a platform to maximize dissemination of resources and build relationships with new academic or industrial partners. NIGMS has a portfolio of investigator-initiated research and small business grants to elucidate novel biosynthetic strategies for bioengineering of natural products and analogs' production. NIGMS also has an emerging interest in identifying the natural products produced by microbial communities and essential for communication within or with a host, such as the symbiotic relationships in the human microbiome (see the microbiome section in this chapter for more NIH updates in this field).[1364]

[1358] http://www.rsna.org/qiba/.
[1359] https://ncats.nih.gov/pubs/features/irb-reliance/.
[1360] https://ncats.nih.gov/pubs/features/ctsa-act.
[1361] https://biospecimens.cancer.gov/researchnetwork/projects/.
[1362] https://www.genome.gov/27540473/electronic-medical-records-and-genomics-emerge-network/.
[1363] https://gnpn-genome.org/.
[1364] http://grants.nih.gov/grants/guide/pa-files/PA-15-135.html.

Data Science and Computational Science

NIH is dedicated to harnessing the potential of the computational and quantitative sciences to elevate the impact and efficiency of biomedical research. New tools, data, and methods are taking biomedicine further than was ever possible before.

Investments in computational biology focus on utilizing optimal techniques in computer and data sciences to address problems in biology and medicine. In FY 2015, NIGMS supported computational research to understand molecular and cellular processes that underpin complex organ function. By funding areas of science that integrate and analyze diverse sets of experimental data, together with computational simulations, researchers were able to pinpoint the inner workings of cellular tissues at extraordinary detail and capture nanoscale biological processes in real time.

In FY 2015, the NLM Evolutionary Genomics Research Group collaborated with researchers at the Broad Institute to identify three new CRISPR-Cas systems (provisionally termed C2c1, C2c2, and C2c3) that could potentially be used for novel genome editing applications. CRISPR, a key component of a system used by bacteria to defend themselves against viruses, is a revolutionary genomic development that allows researchers to make precise changes to the genomes of living cells efficiently and reliably. The group identified the new CRISPR-Cas systems by using bioinformatics approaches to search and analyze data in NLM genomic databases. By modifying the search algorithms, the researchers anticipate discovering even more CRISPR-Cas mechanisms for gene editing.[1365,1366]

NLM scientists work with multiple sources of de-identified prescription and patient outcome data, applying knowledge of clinical terminology, natural language processing, and NLM's terminology resources and tools. In FY 2015, scientists obtained a large dataset from the Centers for Medicare & Medicaid Services' Research Data Enclave for studies about epidemiology of drug–drug interactions, including a study of association between simvastatin use and dementia/Alzheimer's disease. In addition, research on predicting patient outcomes from patient factors was initiated using MIMIC-III (Medical Information Mart for Intensive Care III), the latest version of a large deidentified database of intensive care data from the Massachusetts Institute of Technology, covering nearly 58,000 hospital admissions for more than 48,000 distinct patients. Also in FY 2015, NLM and NIDDK researchers collaborated to identify strategies for better managing chronic kidney disease through EHRs and extrapolated the lessons learned as a model for improving chronic disease care.

In 2014, NCATS Toxicology in the 21st Century (Tox21) program launched a global crowdsourcing prize competition to develop computational models that can better predict chemical toxicity. The models from the seven winning teams, announced in 2015, will become part of Tox21's arsenal of tools that help researchers assess how various chemicals might disrupt biological processes in the human body and lead to negative effects.[1367]

[1365] Ran FA, et al. *Nature* 2015;520(7546):186-191. PMID 25830891.
[1366] Makarova KS, et al. *Nat Rev Microbio* 2015;13(11):722-736. PMID 26411297.
[1367] https://ncats.nih.gov/news/releases/2015/tox21-challenge-2014-winners.

NIMH, together with the National Alliance for Research on Schizophrenia and Affective Disorders and the Netherlands Genetic Computing Cluster, supports the Psychiatric Genomic Consortium (PGC),[1368] the purpose of which is to conduct meta- and mega-analyses of GWAS data, with a focus on five psychiatric disorders: autism spectrum disorder, attention-deficit hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia. NIMH's Research Domain Criteria (RDoC)[1369] is a groundbreaking research framework for studying mental disorders across the lifespan. RDoC integrates many levels of information, from genomics to self-report, to better understand the basic dimensions of functioning that underlie the full range of human behavior and the associated neural circuitry.

Several NIH ICs (NINDS, NIMH, NIDA, and NIBIB) collaborated to establish the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC),[1370] which provides access, information, and a mechanism for providing feedback regarding neuroimaging informatics tools and resources. In FY 2014 and 2015, two new entities were added to the centralized web-based repository, the initial NITRC suite where people could share their software tools and resources with others. The NITRC-Image Repository (NITRC-IR) was established to provide a repository for imaging and other anonymized medical data acquired by federally funded researchers and stored in a standardized format. The NITRC-Computational Environment (NITRC-CE) uses a cloud-based environment to allow scientists around the world to access computational power and thus take full advantage of the other two NITRC components.

Collaborations and Partnerships

NIH's partnerships and collaborative efforts with other federal agencies, foreign governments, the nonprofit sector, industry, and academia are vital to furthering biomedical research and transforming fundamental scientific findings and technical information into effective, knowledge-based approaches that advance public health, including interventions, protective health policies and regulations, and public health campaigns. In FY 2014 and FY 2015, NIH ICs had initiated and maintained many collaborations and partnerships across NIH's portfolio. Many of these are specific to a research area, or disease, and have been described at the appropriate point in this chapter. Some additional collaborations are illustrated here.

Many NIH collaborations involve several ICs. For example, nine NIH ICs (NINDS, NCCIH, NIAAA, NICHD, NIDA, NIMH, NIDCD, NEI, and NIBIB) are involved in a joint initiative with the U.S. National Science Foundation (NSF) and the German Federal Ministry of Education and Research to Support Collaborative Research in Computational Neuroscience. This initiative supports innovative, collaborative science and engineering research on brain function, integration of computational models and methods with neuroscience, and emphasis on data sharing. Since 2002, NIH has funded 152 awards to 170 investigators.[1371]

[1368] https://www.med.unc.edu/pgc.
[1369] http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml.
[1370] https://www.nitrc.org/.
[1371] https://grants.nih.gov/grants/guide/notice-files/NOT-MH-14-002.html.

NIH has continued to build fruitful collaborations with industry partners. For instance, in 2014, the NCATS New Therapeutic Uses program built on its pilot phase by announcing a collaboration with AstraZeneca, Janssen Research and Development LLC, Pfizer, and Sanofi to make 26 agents available for drug repurposing—including, for the first time, some that are suitable for exploring pediatric indications. In 2015, NCATS made four new awards totaling $3 million to research treatments for acute myeloid leukemia, gioblastoma, Chagas disease, and type 2 diabetes.[1372] In 2015, through a collaboration with government, academic, and industry researchers and patient groups, NCATS also demonstrated the therapeutic potential of a drug called cyclodextrin for treating Niemann-Pick type C1 disease. The discovery attracted biotech company Vtesse, Inc., to invest in the compound's further clinical development.[1373]

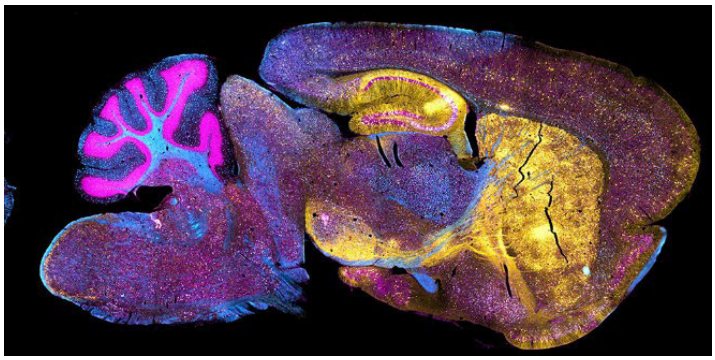

Figure 59. Brain of a mouse with the neurodegenerative disease Niemann-Pick type C1. Credit: I. Williams, NICHD.

NIH also has partners outside of the United States. In March 2014, NIAID, WHO, and the Bill & Melinda Gates Foundation welcomed more than 175 leading scientists, vaccine developers, regulators, and public health officials from around the world as participants at the first Global Vaccine and Immunization Research Forum (GVIRF). This inaugural GVIRF aimed to track recent progress of the Global Vaccine Action Plan's research and development agenda, identify opportunities and challenges, promote partnerships in vaccine research, and facilitate the inclusion of all stakeholders in vaccine research and development. Forum participants discussed scientific and technical challenges in vaccine development, research to improve the impact of immunization, and regulatory issues.[1374]

NIH participates in many collaborations across the U.S. government, particularly with partners within HHS. The annual *Report on NIH Collaborations with Other HHS Agencies*, with its accompanying database,[1375] aims to capture the extent and nature of activities NIH undertakes in collaboration with other HHS agencies and divisions, such as the U.S. Preventive Services Task Force (USPSTF). In support of USPSTF, ODP identifies needs and gaps in prevention research through several ongoing, collaborative activities with AHRQ. To this end, ODP has developed a new website highlighting areas of research

[1372] https://ncats.nih.gov/news/releases/2015/ntu-awards.
[1373] https://www.nih.gov/news-events/news-releases/nih-teams-industry-develop-treatments-niemann-pick-type-c-disease.
[1374] Ford AQ, et al. *Vaccine* 2016;34(13):1489-95. PMID: 26626210.
[1375] For the *Report on NIH Collaborations with Other HHS Agencies for Fiscal Year 2015*, and accompanying database of collaborative activities see: https://report.nih.gov/crs/default.aspx?FY=2015.

where USPSTF has indicated there is insufficient evidence to make a recommendation about a clinical preventive service.[1376] The website acts as a resource for prevention researchers to stimulate new research that will close critical gaps within prevention research.

Within the NIH OD, ODS has taken the lead in developing a National Academies of Sciences, Engineering, and Medicine project to determine guiding principles for inclusion of chronic disease endpoints in future Dietary Reference Intakes. The project builds on a workshop,[1377] panel, and pending publication that ODS co-sponsored in 2015 that discusses scientific issues in using such endpoints and provides options for doing so. The project is a collaborative effort within NIH and with other HHS agencies, USDA, and Health Canada.

In 2014, NIMH and SAMHSA collaborated to foster early intervention for individuals with serious mental illness, which is critical for preventing serious consequences, such as impairment, unemployment, homelessness, poverty, and suicide. The Mental Health Block Grant (MHBG) 5 percent set-aside is a partnership between the federal and state governments to direct five percent of each state's MHBG allocation to support "evidence-based programs that address the needs of individuals with early serious mental illness, including psychotic disorders."

[1376] https://prevention.nih.gov/resources-for-researchers/prevention-research-needs-gaps/uspstf-i-statements.
[1377] https://ods.od.nih.gov/News/DRI_Workshop_March_10-11_2015.aspx.

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, a group of diseases, or an 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 Centers

Establishment of the Alzheimer's Disease Centers

Based on concerns about the scale of the problems posed by Alzheimer's disease (AD), Congress directed NIH to foster further research related to AD in the *PHS Act* of 1984. Under section 445, Congress authorized the establishment of the NIH Alzheimer's Disease Centers (ADCs) program (42 U.S.C. 285e-2). The first ADCs 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. The program's principal objectives are to conduct cutting-edge basic, clinical, translational, and social/behavioral research; train the next generation of researchers; and 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 help researchers 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 ADCs Function Within the NIH Framework

NIH currently funds 30 ADCs (Table 1). Funding for the ADCs comes from NIA through the P30 (center core grant) and P50 (specialized center grant) mechanisms for five years; ADCs compete through a peer review process for additional funding. New applicants for ADC 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. These losses are related to the breakdown of the connections between neurons in the brain and the eventual death of many of these cells. For most people who develop AD, symptoms first appear after age 65. AD and other dementing disorders are caused by disease processes that affect the brain, although age-related brain and body changes can also affect the timing and progression of AD and other dementias.

AD probably has no single 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, although there has been very limited information from clinical trials to directly address the effectiveness of interventions for these conditions on cognitive decline and dementia. Although scientists have learned a great deal about AD, they still do not know what causes the disease and have not identified a cure.

Burden of Illness

More than 5 million Americans, most of them age 65 or older, suffer from AD, and experts agree that these numbers will increase significantly if current U.S. demographic trends continue and no effective prevention 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 five-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 five years of life, total health care spending for people with dementia was more than $0.25 million dollars per person, 57 percent greater than costs associated with death from other diseases, including cancer and heart disease.[1378] 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—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.

[1378] Kelley AS, et al. *Ann Intern Med* 2015;163(10):729-36. PMID: 26502320.

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)*.[1379] 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 to improve services for people with the disease and their families.[1380] 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 development of this budget include:

- 2012 and 2015 Alzheimer's Disease Research Summits
- A 2013 conference on Alzheimer's Disease-Related Dementias (a second conference was held in 2016)
- A 2013 meeting on Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome

The ADC 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. ADCs also foster the development of new research approaches and provide training opportunities for research fellows and junior faculty interested in conducting interdisciplinary AD research. By pooling resources and working cooperatively with each other, ADCs have produced research findings and resources that would have been impossible for investigators working alone.

The ADC program includes two types of centers. All ADCs contain administrative, clinical, data management and statistics, education and information transfer, and neuropathology components, known as "cores," and some centers support other cores by providing specialized resources, such as

[1379] http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf.
[1380] http://aspe.hhs.gov/2014-national-alzheimers-disease-plan-available.

neuroimaging or genetic data. The Alzheimer's Disease Core Centers provide investigators within and outside the ADC program with access to the broad spectrum of ADC resources, while Alzheimer's Disease Research Centers conduct research projects in addition to providing core resources. Some ADCs also support satellite diagnostic and treatment clinics to help recruit patients from underrepresented groups.

Resources shared among ADCs include each center's brain and specimen banks, which consist of well-characterized specimens collected under standardized protocols. ADCs have provided biological samples from patients with AD for hundreds of projects not funded by ADCs.

One of the major shared resources is the Indiana University–hosted National Cell Repository for Alzheimer's Disease (NCRAD), which collects and stores blood, DNA, and cell lines, as well as well-documented phenotypic data (including age and gender) from families with several members affected by AD and from unaffected control participants. The repository is part of 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 genome-wide association studies 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 ADCs have helped create additional collaborative research resources and projects, including the National Alzheimer's Coordinating Center, the Alzheimer's Disease Cooperative Study, and the Alzheimer's Disease Neuroimaging Initiative. 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 30 years stems from research conducted at or resources provided by the ADCs. ADC scientists have conducted a significant amount of the research on protein processing related to plaque and tangle formation in the brain, hallmarks of AD. ADC researchers have also identified the common properties of the abnormal proteins associated with several neurodegenerative diseases. In recent years, ADC 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. ADC researchers have also identified factors that contribute to changes in cognitive abilities, such as social and physical activity.

Currently, many ADCs 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. ADC researchers are also examining relationships and commonalities between AD and cerebrovascular

disease or other neurodegenerative diseases, as well as contributions by co-existing non-neurological conditions that occur in people with AD. In addition, the ADCs 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 ADCs is to recruit racially and ethnically diverse research participants for AD research. To achieve this goal, NIH created the Satellite Diagnostic and Treatment Clinics and linked them to the ADCs. There are 12 active Satellite Clinics recruiting African American, Hispanic, Native American, and Asian participants. National Alzheimer's Coordinating Center data now show that approximately 20 percent of people enrolled in the ADCs are minorities. Also, the ADCs conduct research on specific concerns related to underserved populations, in cooperation with the NIH-supported Resource Centers on Minority Aging Research.

All ADCs have Outreach, Recruitment, and Education Cores (ORECs) that provide research training for new investigators, as well as outreach to the public. OREC efforts have also been redefined to facilitate participant recruitment for large-scale national projects, such as NIA's Genetics Initiative, Alzheimer's Disease Cooperative Study, and Alzheimer's Disease Neuroimaging Initiative. Collaborations include ongoing interactions with organizations such as the Alzheimer's Association, the HHS Administration on Aging, and NIH's Alzheimer's Disease Education and Referral Center. The ADCs 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.

NIH Funding for FY 2014 and FY 2015

NIH funding for the ADCs was $51.32 million in FY 2014 and $55.34 million in FY 2015.

FY 2014 and FY 2015 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments for the ADCs include the following examples:

National Alzheimer's Coordinating Center (NACC)

In 1999, NIH established NACC to facilitate collaborative research and standardize procedures among the ADCs. NACC developed and maintains a large database of standardized clinical and neuropathological research data collected from each ADC. 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 ADCs. A minimum dataset of 67 variables collected from the ADCs contains data on more than 74,000 people enrolled since 1984. A much richer longitudinal uniform dataset (comprising 725 variables) has been collected from nearly 30,000 participants enrolled since 2005. NACC itself has funded 30 collaborative

multicenter studies and junior investigator awards to use NACC data, and nearly 200 additional research studies funded by other sources have used NACC data in their research.

In 2013, NACC began accepting voluntary contributions of brain images from ADCs. More than 2,000 images, including those of participants from underrepresented groups, are now included in the database. These images are linked with the Uniform Dataset already collected on all participants and can now be linked to the genotype data from ADGC (when that is available and appropriate consent has been obtained). Further information is available on the NACC website.[1381]

Today, the NACC database is one of the largest and most comprehensive databases of its type in the world. Data collected by NACC is freely available for all scientists to use in research studies. In 2013, NACC data became available 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 Disease Cooperative Study (ADCS)

ADCS is the large clinical trials consortium that is the cornerstone of NIH's major AD clinical trials effort. The consortium expanded from the ADCs and now includes sites throughout the U.S. and Canada. All current ADCs are performance sites for ADCS. The clinical research outcomes of ADCs are inextricable from the outcomes of ADCS. NIH developed ADCS to advance research on therapeutics that might be useful for treating patients with AD, improve cognition, slow the rate of decline, delay the appearance of AD, or ameliorate behavioral symptoms. In particular, ADCS focuses on interventions that industry might not develop, including agents that lack patent protection or are under patent protection but marketed for other indications, as well as novel compounds developed by individuals, academic institutions, and drug discovery units. More recently, ADCS investigators have begun to explore the use of nonpharmacologic interventions. Moreover, the ADCS mission includes the design of new instruments for use in clinical studies and the development of innovative new approaches to clinical study design and AD clinical study analyses.

Funding for ADCS was renewed in 2013. Building on recent exciting discoveries from the Alzheimer's Disease Neuroimaging Initiative, ADCS focuses on trial approaches that use imaging and other biomarkers in cerebrospinal fluid and plasma to identify participants with AD pathology and to track disease progression and treatment response. ADCS investigators are also conducting prevention studies, particularly in at-risk but presymptomatic individuals. Additionally, ADCS investigators are evaluating the effects of a nonpharmacologic intervention—exercise—in individuals with mild cognitive impairment in a large multisite trial called EXERT (Exercise in Adults With Mild Memory Problems).[1382]

Alzheimer's Disease Neuroimaging Initiative (ADNI)

[1381] https://www.alz.washington.edu/WEB/mri_main.html.
[1382] https://clinicaltrials.gov/ct2/show/NCT02814526.

Most ADCs participate in ADNI, an innovative public–private partnership that is examining the potential of serial MRI, PET, and/or tests of other biomarkers to measure the development and progression of mild cognitive impairment and AD earlier and with greater sensitivity. As is true of ADCS, ADNI's activities and outcomes are inextricable from those of the ADCs. ADNI completed its first enrollment phase in August 2007 and is now using MRI and PET imaging and laboratory and cognitive tests to monitor participants. This stage will generate a comprehensive database that will serve as an important public resource to spur further research. Many of the tools and methods developed by the study are fueling similar efforts in Japan, the European Union, and Australia.

In 2009, funding from the *American Recovery and Reinvestment Act* enabled ADNI to move into a second phase, ADNI-GO. The ADNI-GO research effort is the first study of its kind to focus on participants who exhibit the earliest signs of memory loss in mild cognitive impairment, thought to be a precursor to AD. While the ADNI-GO project work continues, the overall ADNI effort has moved into a third phase, known as ADNI2, building on the successes of earlier ADNI phases to identify the earliest signs of Alzheimer's disease.

Research Activities and Outcomes

Since the establishment of the ADC 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 ADC research.[1383] 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 ADC program has demonstrated tremendous success in facilitating collaborations across institutions, and collaborative multi-ADC research articles are consistently cited more frequently than AD articles overall.

Research accomplishments include the following important studies performed by ADC scientists, highlighting research carried out by several centers. These are only a few examples from a wide range of research studies conducted by the ADCs, and they demonstrate the breadth of research the ADCs support:

- *Unobtrusive monitoring.* Investigators at the Oregon Health & Science University ADC have developed new technologies for real-time in-home monitoring of older individuals' activity patterns and behaviors, such as sleep, medication adherence, movement patterns, and social engagement (e.g., telephone calls, visitors). Changes in activity or behavior can suggest cognitive or physical decline and signal the need for intervention. This technology may also provide another means of monitoring treatments for AD and related dementias. The monitoring technology is providing an unprecedented body of data on how health and behavior change over time with advancing age. This system has been placed in nearly 500 homes, with most users balancing the privacy concerns raised by this sort of full-time monitoring against the enhanced security the system provides, as well as the knowledge that findings from this

[1383] Hughes ME, et al. *JAMA Neurol* 2014;714:412-20. PMID: 24514750.

research could benefit many other people striving to maintain their independence for as long as possible.[1384]

- *Racial differences in AD pathology.* For a variety of reasons, investigators often have difficulty recruiting diverse populations into research studies. Through careful and sensitive outreach to the community, the research team at the Rush University Medical Center ADC has successfully recruited African American in the Chicago area. In a recent study, the investigators conducted postmortem examinations of the brains of African American and White patients with suspected AD to look for Alzheimer's pathology. The scientists found that the African American patients were more likely to have mixed brain pathologies (e.g., amyloid combined with Lewy bodies and/or small infarcts) than were age-, sex-, education-, and cognition-matched White decedents with Alzheimer's dementia. These findings suggest that therapies targeting amyloid alone may not work as well in African Americans, underscoring the importance of developing new treatments that target other common pathologies, particularly in African Americans, to lessen the burden of AD dementia.[1385]

- *Defining the reach of chronic traumatic encephalopathy (CTE).* In addition to Alzheimer's disease, ADC investigators are internationally recognized experts on other forms of dementia. For example, CTE, a progressive neurodegenerative disorder linked to repetitive TBI, shares a pathological hallmark—the presence of tau tangles in the brain—with Alzheimer's and other dementias. The frequency of CTE has been assessed among military veterans and professional athletes but not the general population. Investigators from the Boston University and Mayo Clinic ADCs used brains from a brain bank for neurodegenerative disorders to screen for CTE pathology in the brains of individuals exposed to contact sports and matched controls without such exposure. The scientists identified a small but significant subset of individuals with neurodegenerative disorders and concomitant CTE pathology, which was found only in individuals with a documented history of participation in contact sports. These preliminary findings should be validated in other brain bank cohorts.

- *Differentiating dementia subtypes.* Investigators at the Northwestern University ADC used memory assessments and amyloid imaging to help understand primary progressive aphasia (PPA), a type of dementia usually associated with frontotemporal lobar degeneration, to show that a subset of these patients actually have Alzheimer's pathology—but in a different part of the brain than typical AD patients. This unexpected finding opens new avenues for research on the pathology of Alzheimer's and related dementias.

Recommendations for Improving ADCs' Effectiveness, Efficiency, and Outcomes

Evaluation Plans

[1384] Lyons BE, et al. *Front Aging Neurosci* 2015. PMID: 26113819.
[1385] Barnes LL, et al. *Neurology* 2015;85(6):528-34. PMID: 26180136.

The National Advisory Council on Aging evaluates and makes recommendations for the ADC program every four years. The next evaluation is scheduled for 2017.

Future Directions

NIH plans to have the ADCs 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. In addition, the ADCs will continue to search for biomarkers that predict cognitive decline and diagnose cognitive impairment and dementia.

Table 1. ADCs

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, St. Louis, MO	1985
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
University of California Davis School of Medicine, Sacramento, CA	1991
Indiana University, Indianapolis, IN	1991

Institution and Location	Year Established
Rush University Medical Center, Chicago, IL	1991
University of California, Los Angeles, CA	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

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 15 OAICs (**Error! Reference source not found.**).

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 Career Development Core 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; there is no single disease or condition that 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 loss of sensory function.

Burden of Illness

Currently, more than 40 million Americans are more than 65 years old; of these, nearly 6 million are over age 85, and more than 70,000 have reached 100. By 2030, the number of individuals age 65 or older is likely to reach 70.3 million, comprising 20 percent of the entire U.S. population. The number of the oldest old, people age 85 or older, is expected to grow to at least 20.9 million by 2050.

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:

- 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 other NIA-funded programs and centers (e.g., Resource Centers for Minority Aging Research,[1386] Centers on the Demography and Economics of Aging,[1387] Roybal Centers,[1388] ADCs,[1389] and Nathan Shock Centers[1390])
- 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 2014 and FY 2015

NIH funding for the OAICs was $13.22 million in FY 2014 and $13.09 million in FY 2015.

FY 2014 and FY 2015 Progress Report

Programmatic and Research Activities and Outcomes

- The University of Florida OAIC focuses on sarcopenia (degenerative age-related muscle loss), including biological mechanisms and contributing factors, as well as the prevention and rehabilitation of disability resulting from sarcopenia. University of Florida researchers examine these issues from interdisciplinary perspectives across the entire spectrum of biomedical

[1386] http://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar.
[1387] http://www.nia.nih.gov/research/dbsr/centers-demography-and-economics-aging.
[1388] http://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging.
[1389] http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers.
[1390] http://www.nia.nih.gov/research/dab/nathan-shock-centers-excellence.

investigation, including molecular biology, animal studies, clinical research, behavioral and social sciences, and epidemiology. Notably, Florida OAIC investigators led the LIFE Study, a major clinical trial comparing the effects of a moderate-intensity physical activity program with the effects a health education program on prevention of mobility loss disability in at-risk older Americans. In 2014, the investigators reported that a carefully structured program of moderate physical activity can reduce people's risk of losing the ability to walk without assistance—perhaps the single most important factor in whether vulnerable older people can remain independent.[1391]

- The Boston Medical Center at Boston University has established an OAIC in collaboration with Tufts University and the Joslin Diabetes Center. This OAIC fosters collaborations among the universities' multidisciplinary teams of investigators to improve physical mobility by covering the entire spectrum of drug discovery, from target identification to clinical trials and function-promoting therapies.

- 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 exercise and other interventions to improve balance and mobility, prevent falls, and prevent fall-related injuries.

- Investigators at the Duke University OAIC work to understand and modify different causes of decline in physical functioning. Identifying biomarkers that may predict risk for functional decline is one major focus at the Duke OAIC.

- The Johns Hopkins University OAIC supports research to determine the causes of and potential interventions to reduce frailty in older adults. To support frailty intervention studies, the university created a clinical translation unit and a registry of older adults who might be willing to participate in research.

- The theme of the University of California, Los Angeles (UCLA) OAIC is "Preventing Disease and Disability in Vulnerable Populations: A Translational Approach," and the center's investigators address health disparities that vulnerable older persons face because of (1) inadequate understanding of contributors to health and specific illnesses; (2) lack of effective preventive or therapeutic approaches; and (3) inadequate ability to get needed treatment to vulnerable older populations. Through its commitment to translational research, the OAIC also helps overcome the barriers between the promise of basic science research and the delivery of better health.

- 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

[1391] Pahor M, et al. *JAMA* 2014;311(23):2387-96. PMID: 24866862.

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. Recently, investigators at the Wake Forest OAIC found that diet and exercise—alone or combined—improved exercise capacity in obese older patients with heart failure with preserved ejection fraction, a type of heart failure that is being diagnosed with increasing frequency, particularly among older adults. Although diet and exercise were both effective separately, participants who combined a calorie-restricted diet with regular exercise saw the greatest benefit.[1392]

- 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. Investigators from the Yale and University of California, San Francisco (UCSF) OAICs who are collaborating on research related to diabetes in older individuals found that among older adults with multiple health conditions and functional limitations, the harms of intensive treatment (e.g., increased risk of hypoglycemia, or dangerously low blood sugar) likely outweigh the benefits. Further research is needed to determine the optimal standard of care for older adults with diabetes and other serious health conditions.[1393]

- The University of Michigan OAIC, the first OAIC funded by NIH, advances research on older adults' health care problems. Its research emphases include balance, falls, and mobility, as well as pelvic floor impairment in women. In a recent study supported by this OAIC, investigators implemented a multi-component targeted infection-control program (TIP) in preventing infections and antimicrobial resistance among high-risk nursing home patients, many of whom use indwelling urinary catheters and/or feeding tubes that put them at increased risk of such infections. The researchers found that the intervention was associated with a significant decrease in the overall prevalence of resistant organisms, including MRSA infection, as well as a decrease in clinically defined catheter-associated UTIs. Lessons learned from this effort are being implemented in more than 500 VA and non-VA facilities in all 50 states through a project funded by AHRQ.[1394]

[1392] Kitzman DW, et al. *JAMA* 2016;315(1):36-46. PMID: 26746456.
[1393] Lipsa KJ, et al. *JAMA Intern Med* 2015;175(3):356-62. PMID: 25581565.
[1394] Mody L, et al. *JAMA Intern Med*. 2015;175(5):714-23. Erratum in: *JAMA Intern Med.* 2015;175(7):1247. PMID: 25775048.

- The Mount Sinai School of Medicine OAIC focuses on pain management and palliative care. Ongoing pilot studies are testing interventions to prevent delirium in long-term care settings; evaluating a couple-based intervention to address the pain and symptom management needs of older lung cancer patients and their caregivers; and testing a non-drug intervention for depression among nursing home residents diagnosed with a serious illness.

- The OAIC at the University of Arkansas for Medical Sciences studies the causes of declining skeletal and heart muscle function with aging and is developing new interventions for these conditions by targeting protein metabolism and other approaches. The OAIC represents a unique collaborative effort between the University of Arkansas and the University of Oklahoma Health Sciences Center.

- The 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 in San Antonio. Current pilot projects include both preclinical and clinical studies of several compounds that have demonstrated an ability to extend lifespan through the NIA-supported ITP. For example, one current study explores the safety and efficacy of the immunosuppressive drug rapamycin, shown in the ITP to extend lifespan in mice, can protect physical and cognitive function in older adults. In another study, investigators are working to determine whether the drug metformin prevents or slows the development of frailty in older adults with pre-diabetes.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the OAICs

In 2015, the National Advisory Council on Aging reviewed the NIA Division of Geriatrics and Clinical Gerontology (DGCG), where the OAICs are administratively housed, and made several relevant recommendations, including:

- 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

- Facilitate interaction with NIH-sponsored CTSA programs nationwide

DCGC is currently considering the optimal response to these recommendations.

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 the center's 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 (OAICs).

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[1395]
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994
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 Arkansas for Medical Sciences, Little Rock, AR	2011
University of California, San Francisco, CA	2013
University of Texas Health Science Center, San Antonio, TX	2015

[1395] A Center for the Study of Aging was started at Duke University in 1955; it was redesignated 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

NIAMS, NINDS, and NICHD fund the Wellstone MDCRCs through the U54 Specialized Centers Cooperative Agreement award mechanism (Table 3). 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.

A Steering Committee of NIH science officers and the directors and co-directors of each center coordinates the Wellstone MDCRCs' scientific program. The Steering Committee promotes collaborations among center investigators, sharing of resources, and exchange of scientific information.

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 is the most common childhood form of muscular dystrophy and is an X-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 (in females, there are 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, while 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.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Treatments such as physical therapy, use of devices for support, corrective orthopedic surgery, and drugs can reduce symptoms and improve quality of life for some individuals. Some drugs, such as corticosteroids, can slow the progression of DMD to some extent but have adverse side effects. A variety of 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. Although FDA has reviewed or is in the process of reviewing a few applications for new drug approvals, none have met the thresholds of safety and efficacy for approval. But 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 Duchenne or Becker muscular dystrophy.[1396] Myotonic dystrophy affects approximately 1 in 8,000 people worldwide.[1397] FSHD affects approximately 1 in 20,000 people and affects men and women equally.[1398]

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 2014 and FY 2015 follow:

- At the University of Rochester center, 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 center 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 LGMDs, CMDs, and Miyoshi myopathy.

- In FY 2015, the center funded through the University of Pennsylvania moved to the University of Florida. This center successfully re-competed for funding in FY 2015, with investigators from the University of Florida, Northwestern University, and the UCLA comprising the current center. Projects 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 Nationwide Children's Hospital Research Institute in Columbus, Ohio, for which funding ended in FY 2015, focused on strategies to detect immune responses in

[1396] https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy.
[1397] http://ghr.nlm.nih.gov/condition/myotonic-dystrophy.
[1398] https://ghr.nlm.nih.gov/condition/facioscapulohumeral-muscular-dystrophy.

patients that can occur when DMD-causing mutations are corrected and whether these immune responses may be involved in the success or failure of gene correction therapies.

- The Wellstone MDCRC at the University of Massachusetts continues to partner with investigators at Children's Hospital in Boston on studies of molecular, genetic, and epigenetic pathologies of FSHD, with the goal of developing potential therapies that can be tested clinically.

- 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, which began in its current form in FY 2014, 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 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 2014 and FY 2015

NIH funding for the Wellstone MDCRC program was $8.8 million in FY 2014 and $9.0 million in FY 2015.

FY 2014 and FY 2015 Progress Report

Programmatic Activities and Outcomes

The University of Washington partnered with the Fred Hutchinson Cancer Research Center to join the Wellstone MDCRC network in FY 2014. In FY 2015, investigators at the University of Florida and University of Iowa Wellstone MDCRCs competed successfully for renewal. At the new UT Southwestern center, a collaboration with the university's neuromuscular cardiomyopathy clinic has received funding from NHLBI for the next five years.

Although funding for the Nationwide Children's Hospital Research Institute MDCRC ended in FY 2015, many of the center's investigators continue to use support from other grants to explore possible gene therapies for muscular dystrophies and other neuromuscular disorders. Ongoing work includes an NIAMS-funded Phase I clinical trial to test the safety and tolerability of a novel therapeutic transgene in a first-in-human study[1399] and a different gene therapy strategy that attempts to target a wider variety

[1399] https://clinicaltrials.gov/ct2/show/NCT02704325.

of muscles in a DMD mouse model.[1400] Moreover, Nationwide Children's Hospital Research Institute remains eligible to compete for a future Wellstone MDCRC grant.

The Wellstone MDCRC program has provided opportunities for public–private partnerships in muscular dystrophy. Projects have involved collaborations with or additional support from companies such as Ionis Pharmaceuticals,[1401] Biogen, and Genzyme/Sanofi. The centers also have strong ties with patient advocacy groups and voluntary health organizations that promote and support muscular dystrophy research. For example, UT Southwestern's neuromuscular clinic is partially supported by the Muscular Dystrophy Association, the FSH Society plays a large role in the University of Massachusetts Wellstone MDCRC, and Parent Project Muscular Dystrophy provides supplemental funding to the University of Florida center. Recognizing that input from patients and their families strengthens the Wellstone MDCRC program, NIH required that all centers competing for FY 2014 and FY 2015 funding articulate plans for community outreach and involvement.

Because training and career development is an important component of the Wellstone MDCRC program, all centers supported in FY 2014 and FY 2015 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.

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.[1402] 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 University of Rochester's National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy, which contains information about more than 2,100 patients, provides researchers with cell and tissue samples and clinical information about the donors of these samples. Between 2009 and 2014, the registry facilitated 19 clinical studies by 15 different investigators at 11 research sites.[1403]

- 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 that investigators will provide to other scientists upon request.

[1400] https://projectreporter.nih.gov/project_info_description.cfm?aid=8879230&icde=30530160.
[1401] https://clinicaltrials.gov/ct2/show/NCT02312011.
[1402] http://www.wellstonemdcenters.nih.gov/index.htm.
[1403] https://www.urmc.rochester.edu/MediaLibraries/URMCMedia/neurology/documents/2014-Newsletter.pdf.

- 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 labs studying FSHD or other muscular dystrophies.

- 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 new UT Southwestern Wellstone MDCRC is establishing a comprehensive electronic database that investigators can use to optimize exon-skipping strategies to rescue dystrophin expression in 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 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 2014 and FY 2015 are provided below:

- The University of Rochester MDCRC has made advances in preclinical therapy development and clinical trial readiness that collectively improve the environment for new therapies for myotonic dystrophy. Investigators have shown preclinical efficacy of antisense oligonucleotides in blocking or eliminating the toxic RNA that forms the basis for myotonic dystrophy. This MDCRC-supported work fostered a collaboration on antisense oligonucleotide therapeutics with funding from NIH, Isis Pharmaceuticals (now Ionis Pharmaceuticals), and Biogen. Investigators filed an IND with FDA and began recruiting people for a Phase 1/2 clinical trial.[1404]

- The University of Iowa MDCRC has led important breakthroughs in the molecular mechanisms of the dystroglycanopathies.[1405, 1406] The Iowa MDCRC is also addressing clinical trial readiness, to ensure that sufficient tools (e.g., biomarkers, trial endpoints) and knowledge (natural history) are in place for safety and efficacy clinical trials in human subjects. For example, the group published data demonstrating that dystroglycanopathy symptoms can include urologic and

[1404] https://clinicaltrials.gov/ct2/show/NCT02312011.
[1405] Inamori K, et al. *J Biol Chem* 2014;289(41):28138-48. PMID: 25138275.
[1406] Bharucha-Goebel DX, et al. *Neurology* 2015;4(14):1495-7. PMID: 25770200.

gastrointestinal dysfunction and that questions about these treatable conditions should be incorporated into routine care.[1407]

- Investigators at the University of Florida Wellstone MDCRC are refining methods to assess skeletal muscle health in patients with muscular dystrophies, using MRI and spectroscopy.[1408] In 2014, investigators began recruiting patients for a study to develop and validate MRI and spectroscopy methods that can predict changes in cardiac and respiratory muscle function in boys who have DMD.[1409] MRI and spectroscopy biomarkers developed through research initiated by this Wellstone center are currently used in DMD clinical trials. Wellstone MDCRC researchers are also conducting preclinical studies of potential anti-inflammatory treatments for DMD.[1410]

- In 2015, researchers at the Nationwide Children's Hospital Wellstone MDCRC published results from a six-patient gene transfer study for . Four of the six participants showed improved walking ability and structural improvements in their leg muscle, while the other two showed no improvement. No adverse events were observed.

- Building on discoveries about the molecular mechanisms responsible for FSHD, researchers at the University of Massachusetts Wellstone MDCRC are learning how changes in the expression of disease-causing genes alter cells' abilities to remove intracellular proteins.[1411] The researchers are continuing to identify and test candidate biomarkers that could assess how cells, animals, and, ultimately, patients respond to possible therapeutic compounds.[1412]

- Wellstone MDCRC investigators at the University of Washington and the Fred Hutchinson Cancer Research Center published data about an RNA-transfer approach that interferes with the formation of toxic RNA in a mouse model of myotonic dystrophy type 1.[1413] The researchers are also developing an MRI tool to noninvasively monitor the effects of gene transfer approaches in animals.[1414]

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDCRCs

The muscular dystrophy research community has reached a watershed moment. In 2015, for the first time ever, three potentially disease-modifying therapies were presented as new drug applications to FDA. While none of the applications have been approved yet, the results of clinical trials underscore the

[1407] Crockett BS, et al. *Neurology* 2015;84(5): 532-9. PMID: 25568299.
[1408] Lott DJ, et al. *Neuromuscul Disord* 2014;24(7):574-82. PMID: 24798221.
[1409] https://clinicaltrials.gov/ct2/show/NCT02195999.
[1410] Ceco E, et al. *Sci Transl Med* 2014;6(259):259ra144. PMID: 25338755.
[1411] Homma S, et al. *Ann Clin Transl Neurol* 2015;2(2):151-66. PMID: 25750920.
[1412] Jones TI, et al. *Clin Epigenetics* 2015;7(1):37. PMID: 25904990.
[1413] Bisset DR, et al. *Hum Mol Genet* 2015;24(17):4971-83. PMID: 26082468.
[1414] Park J, et al. *PLoS One* 2015;10(4):e0124914. PMID: 25856443.

need for more work on robust and objective clinical trial outcome measures and biomarkers to measure the effects of candidate therapeutics. Developing and validating these biomarkers and outcomes will continue to be a point of emphasis in Wellstone MDCRC solicitations going forward.

In addition to longer-range endeavors such as gene therapy and gene editing that have the potential to address the root cause of disease, other strategies are being developed to address secondary aspects of muscular dystrophies, such as muscle oxidative stress, inflammation, fibrosis, or reduced regeneration. While candidate therapeutics that target these secondary conditions may themselves have positive impacts on the disease, combining these candidate therapeutics with strategies like exon-skipping or gene replacement may result in synergistic effects. Research in animal and cell models will help determine which combinations of candidate therapeutics should eventually be tested in clinical trials. The Wellstone Centers may provide appropriate environments for testing these combination therapies.

Similarly, as improvements in standard of care continue to lengthen the life of patients with muscular dystrophy, effects on non-skeletal muscle systems and tissues are becoming more problematic for patients. In addition to the cardiac issues that contribute significantly to mortality in many muscular dystrophies, effects on the skeletal, nervous, visual, gastrointestinal, and endocrine systems—from either the dystrophies themselves or the therapies used to treat them—significantly affect the quality of life of people living with muscular dystrophy. Targeting the multisystemic nature of the muscular dystrophies will be a new area of emphasis for the next Wellstone MDCRC solicitation.

Since they involve some of the top clinical research and care sites in the nation for muscular dystrophy patients, the Wellstone Centers will also be encouraged to conduct studies to optimize care and services for individuals living with muscular dystrophies. Important research topics include the most effective strategies for transitioning between pediatric and adult care as patients grow up, optimizing care for secondary conditions, facilitating access to medical equipment, and coordinating clinical care between regional centers and less-specialized local facilities. The Wellstone MDCRCs will continue to focus on community outreach, training, and research that spans the spectrum from basic science to clinical research, because work remains in these critical areas.

Future Directions

NIH is committed to supporting up to six outstanding Wellstone MDCRCs. Based on its funding commitment to the existing Centers, NIH is likely to hold an open competition and to fund up to three Centers (for a total of up to six active Centers) in FY 2018, pending the availability of funds and a sufficient number of highly meritorious applications. Applicants will be encouraged to consult the Action Plan for the Muscular Dystrophies,[1415] a consensus document developed by the interagency Muscular Dystrophy Coordinating Committee[1416] with input from patients, advocacy groups, basic scientists, clinicians, and Federal agencies that highlights many of these scientific opportunities and the need for broad cooperation in seeking effective treatments for the muscular dystrophies. Grantees will join the

[1415] https://mdcc.nih.gov/action_plan/index.htm.
[1416] https://mdcc.nih.gov.

network of Wellstone MDCRCs to translate scientific findings and technological developments into treatments and other health-related improvements for people with muscular dystrophies.

NIH also supports multi-project grants and core centers for muscular dystrophy research at academic institutions that are not Wellstone MDCRCs. NIH is promoting interactions among investigators at the Wellstone MDCRCs and these other institutions to expand the scope and strength of the Wellstone network.

Table 3. Active Senator Paul D. Wellstone MDCRCs, FY 2014–2015.

Institution and Location	Years Funded
University of Rochester, Rochester, NY	2003–present
University of Iowa, Iowa City, IA	2005–present
University of Pennsylvania, Philadelphia, PA/University of Florida, Gainesville, FL	2005–present
Nationwide Children's Hospital Research Institute, Columbus, OH	2010–2015
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 for addressing and ultimately eliminating 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.[1417] The statute specifically mandated the creation of COEs in research institutions for the purpose of conducting biomedical and behavioral 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 and/or ethnic group who is socially disadvantaged and/or subject to potential discriminatory acts. Minority health populations are classified by the Office of Management and Budget (OMB) Directive 15 into the following racial and ethnic categories: American Indian or Alaska Native, Asian, Black or African American, Hispanic/Latino, and Native Hawaiian or Other Pacific Islander.

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/prevalence, burden of disease (e.g., disability-adjusted life year [DALY]), premature and/or excessive mortality in diseases where populations differ, poorer health-related quality of life, and/or worse daily functioning, according to standardized measures and self-reports.

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; stress; smoking; obesity; racism/discrimination; unhealthy environmental conditions; low education; low SES; limited language proficiency; poor

[1417] 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).

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: quality indicators of health services (e.g., differential treatment results, poor physician/patient communication, different treatment offered, poor management of co-morbidities, poor symptom management, adverse events to 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 and low-SES and rural groups 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.

NIMHD COEs address health disparities through the following strategies:

- Conducting and supporting basic, clinical, social sciences, health services, 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[1418] and the National Prevention Strategy.

Since 2002, NIMHD has supported 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

[1418] http://www.minorityhealth.hhs.gov/npa/templates/content.aspx?lvl=lvlid=33&ID=285.

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 longstanding partnerships with local and regional communities and organizations addressing health disparities. The R24 mechanism, which NIMHD no longer uses, enabled institutions with emerging or modest research infrastructures to begin building research capacity to address health disparities. Several institutions that received these R24 awards have since successfully established NIMHD COEs using the P20 mechanism.

NIMHD supported 49 COEs in FY 2014, including 46 ongoing (noncompeting) awards and 3 competing awards, and 45 COEs in FY 2015, including 40 ongoing (noncompeting) awards and 5 competing awards. All COEs funded since 2005 have had project periods of five 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, Hispanic-serving institutions, tribal colleges/universities, and liberal arts colleges. 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/or 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 initial NIMHD COEs were focused on health disparities associated with cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity. Subsequent NIMHD solicitations for COEs have broadened the focus to encompass any diseases or conditions that disproportionately affect health disparity populations.

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 America'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, cardiovascular disease, 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 NIH Health Disparities Strategic Plan and Budget,[1419] the scope of activities conducted by NIMHD COEs includes research, development of research capacity (including training and education), and community outreach. 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
- A research core for conducting, coordinating, generating, and advancing research on health disparities
- A research training and education core for conducting and advancing research training
- A community engagement core for engaging communities and others as partners in eliminating health disparities through community participation in research and the joint development and dissemination of effective health information messages and research findings

NIH Funding for FY 2014 and FY 2015

NIH funding for the NIMHD COE program was $51.7 million in FY 2014 and $47.5 million in FY 2015.

FY 2014 and FY 2015 Progress Report

Programmatic Activities and Outcomes

Significant programmatic accomplishments include the establishment of eight new COEs and eight competing renewals. There were 49 active NIMHD COEs in FY 2014 and 45 in FY 2015 (Table 4).

Research Activities and Outcomes

Funding for the NIMHD COEs has produced a number of research accomplishments for FY 2014 and FY 2015.

The University of Michigan COE worked in collaboration with Jackson Heart Study researchers to integrate social and biological factors in understanding the determinants of minority health and health disparities. A recently published study in 5,301 African Americans investigated the relationship between individual-level socioeconomic position (SEP) and neighborhood characteristics with sleep duration and quality. The research found that social and environmental characteristics are associated with sleep

[1419] https://www.nimhd.nih.gov/about/overview/strategic-plan.html.

duration and quality in African Americans: Low SEP was associated with higher odds of long sleep, while higher neighborhood violence was associated with poorer sleep quality. Lower education and lower income were associated with greater odds of long sleep and poorer sleep quality compared with higher education and high income.[1420]

The North Carolina Central University COE addresses racial and ethnic disparities in end-stage renal disease (ESRD). Research projects provide evidence that gender differences in ESRD may be the result of a higher prevalence of undiagnosed and or untreated prediabetes among African American men than among African American women. Diabetes screening samples from an African American cohort revealed that men were at a higher risk than women of developing diabetes. These results support the researchers' hypothesis that African American men may be more predisposed to prediabetes kidney injury than their female counterparts are. The researchers recommend that young African American men should be screened for biomarkers of kidney injury even if they have normal glucose and blood pressure levels.[1421]

The University of Miami COE is conducting dissemination and implementation research to address racial and ethnic disparities in behaviorally rooted health conditions, including HIV/AIDS, substance use, and intimate partner violence. One research project evaluates the effectiveness of an evidence-based intervention, developed and tested by the COE, that is delivered in community public health settings and designed to reduce HIV risk behaviors and STI incidence in low-income Hispanic women. Initial findings indicate that the intervention increases communication about HIV risks between women and their partners, reducing the risk of HIV infection and also reducing the levels of interpersonal violence the women reported experiencing.[1422]

The George Washington University COE is conducting work to better understand factors contributing to health disparities specific to Latino immigrants. The primary research effort is to collaborate with Latino community partners to implement and evaluate an innovative, multi-level community-driven intervention called *Adelante* that promotes positive youth development, to prevent substance use and co-occurring conditions in youth and families. Accomplishments include research that engaged local Latino youth and resulted in the development and filming of a six-episode webnovela, *Victor and Erika.*[1423] The webnovela serves both as an intervention component and as a community engagement tool to build awareness of and promote *Adelante*.

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 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

[1420] Johnson DA, et al. *Sleep* 2016;39(9):1749-59. PMID: 27253767.
[1421] Pointer MA, et al. *Front Public Health* 2015;3:7. PMID: 25674558.
[1422] https://projectreporter.nih.gov/project_info_description.cfm?aid=8842469&icde=0.
[1423] https://www.youtube.com/playlist?list=PLv2oWILP0yQ28U7wfgtgGAEhEn3Llj9xf.

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. In FY 2016 and FY 2017, NIMHD will continue to pursue ongoing recommendations, including efforts to:

- Increase the diversity of the scientific workforce, especially the number of women and biomedical and behavioral scientists from racial and ethnic and other health disparity populations. Focused efforts are particularly important for increasing the number of female 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) 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 social 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.

Evaluation Plans

NIMHD program staff evaluate the COEs' annual progress by examining each COE's published peer-reviewed articles, books, and book chapters; 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 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 diverse 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.

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 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. 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.

Table 4. NIMHD Centers of Excellence Active in FY 2014-15.

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
Dillard University, New Orleans, LA
Florida Agricultural and Mechanical University, Tallahassee, FL
Florida International University, Miami, FL
George Washington University, Washington, DC
Georgetown University, Washington, DC
Georgia Southern University, Statesboro, GA
Georgia State University, Atlanta, GA
Harvard School of Public Health, Boston, MA
Howard University, Washington, DC
Jackson State University, Jackson, MS

Institution and Location
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
SUNY Downstate Medical Center, Brooklyn, NY
University of Alabama, Birmingham, AL
University of Arizona, Tucson, AZ
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 Kansas Medical Center, Kansas City, KS
University of Maryland, College Park, MD[1424]
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 Carolina, Greensboro, NC
University of North Texas Health Sciences Center, Fort Worth, TX

[1424] Originally located at the University of Pittsburgh.

Institution and Location
University of Oklahoma Health Sciences Center, Oklahoma City, OK
University of Pennsylvania, Philadelphia, PA
University of South Alabama, Mobile, AL
University of South Carolina, Columbia, SC
University of South Dakota, Vermillion, SD
University of Southern California, Los Angeles, CA
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

Translation of fundamental research into interventions for treating rare diseases is a daunting task. There are more than 6,500 rare diseases, but there are FDA-approved treatments for only a few hundred. Although the pace of rare disease therapeutics development has increased in recent years—of the drugs approved by FDA in 2015, almost half were for rare disorders—the approach of addressing and resolving one disease at a time takes too long. NCATS' approach to translational science is not only to look for and address unique characteristics about a disease but also to recognize commonalities across diseases, including rare diseases. By identifying shared molecular biology, signaling pathways, and other common characteristics across several diseases, scientists may be able to accelerate the development of treatments for multiple diseases at once.

RDCRN was established in 2003 by the NIH ORDR, in collaboration with six NIH ICs. RDCRN is a collaborative model of rare diseases research that includes patient advocacy groups as research partners. RDCRN facilitates clinical research in rare diseases through support of (1) collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, and trials; (2) training of clinical investigators in rare diseases research; (3) pilot and demonstration clinical research projects; and (4) access to information related to specific rare diseases for basic and clinical researchers, academic and practicing physicians, patients, patients' families and friends, and the public. NCATS assumed responsibility for RDCRN in 2011. In October 2014, the number of consortia involved rose from 19 to 22, and a Data Management and Coordinating Center (DMCC) was added.

A valued feature of RDCRN, the contact registry on the network's website,[1425] connects registered patients with rare diseases to RDCRN so that those patients can be offered clinical research opportunities and updates on the progress of research projects. The site also contains extensive information about ongoing research and information about the diseases being studied. To learn more about the RDCRN consortia and DMCC, visit the NCATS website.[1426]

How RDCRN Functions within the NIH Framework

Each multi-site consortium 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 project scientists, and the chair of the RDCRN Coalition of Patient Advocacy Groups.

[1425] https://www.rarediseasesnetwork.org/registry/.
[1426] https://ncats.nih.gov/rdcrn.

Description of Disease or Condition

A disease is defined as rare if fewer than 200,000 people in the U.S. have it. There are more than 6,500 rare diseases, and just over 400 approved drugs and biologic products are available as treatments. 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. The National Organization for Rare Disorders estimates that about 1 in 10 people in the U.S.—or 25 million to 30 million people—have a rare disease.

The RDCRN website[1427] lists all the current and former consortia. The consortia discussed below were funded for the second phase of 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. Overall, rare diseases are devastating and costly, not only for the patients but also for their families. This is partly because of the diseases' severity and partly because diagnosis can take a long time, often long after symptoms have appeared. Treatment is often unavailable even once a disease is diagnosed. It is difficult to assess the pain, suffering, and lost opportunities experienced by patients and their families. Because of these variables, rare diseases represent a disproportionate share of health care spending. In addition, a limited number of drug companies conduct research into rare diseases, since it is difficult to recover the costs of developing treatments for small, geographically dispersed populations.

Scope of NIH Activities: Research and Programmatic

RDCRN currently supports natural history studies, clinical trials, and other clinical studies on more than 200 rare diseases at more than 260 clinical centers across the U.S. and internationally; 144 patient advocacy organizations and 2,600 researchers are actively participating.

On October 8, 2014, RDCRN was expanded to 22 research consortia and a DMCC:

- Autonomic Rare Diseases Clinical Research Consortium
- Brain Vascular Malformation Consortium
- Brittle Bone Disorders Consortium
- Chronic Graft Versus Host Disease Consortium
- Clinical Research in Amyotrophic Lateral Sclerosis and Related Disorders for Therapeutic Development

[1427] https://www.rarediseasesnetwork.org/.

- Consortium of Eosinophilic Gastrointestinal Disease Researchers
- Developmental Synaptopathies Associated with *TSC, PTEN* and *SHANK3* Mutations
- Dystonia Coalition
- Frontotemporal Lobar Degeneration Clinical Research Consortium
- Genetic Disorders of Mucociliary Clearance Consortium
- Inherited Neuropathies Consortium
- Lysosomal Disease Network
- 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

Descriptions of the consortia and the DMCC can be found on the Consortia webpage.[1428]

Funding and scientific oversight for RDCRN are provided by NCATS and 10 NIH ICs: NICHD, NCI, NHLBI, NIAID, NIAMS, NIDCR, NIDDK, NIMH, NINDS, and ODS within the NIH OD. In addition, patient advocacy groups provide supplemental funds for many of the projects.

NIH Funding for FY 2014 and FY 2015

The collaborations are made possible through awards by NIH, totaling about $29 million in fiscal year 2014 funding alone, with approximately $1.25 million per consortium per fiscal year.

[1428] http://www.ncats.nih.gov/rdcrn/consortia#ard.

FY 2014 and FY 2015 Progress Report

Programmatic and Research Activities and Outcomes

Since 2009, RDCRN has enrolled 43,845 participants in its multisite clinical research studies. Currently, there are over 90 active research studies:

- On March 28, 2015, FDA approved sirolimus (Rapamune) to treat LAM, a rare, progressive lung disease that mostly affects women of child-bearing years. The research conducted by the Rare Lung Diseases Consortium resulted in FDA's approval of sirolimu, the first approval of a drug therapy treatment for LAM.[1429]

- On July 2, 2015, RDCRN's Porphyrias Consortium published an article on the safety and efficacy of afamelanotide in the novel treatment of erythyropoietic protoporphyria, a rare blood disorder.[1430]

- On September 29, 2015, RDCRN's Genetic Disorders of Mucociliary Clearance Consortium published a consensus document on diagnosis, monitoring, and treatment of primary ciliary dyskinesia, a rare lung disorder that can damage the lungs.[1431]

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of RDCRN

Future Directions

The continued commitment of NCATS and the 10 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 disease community and rare disease research is immense.

RDCRN addresses many unique challenges in developing rare disease therapies, including difficulties in diagnosis, widely dispersed patients and scientific experts, and a perceived high risk and cost for developing such treatments. RDCRN has collected data on more than 200 rare conditions, enabling scientists to better understand and learn from the common features among diseases.

The network is a distinctive clinical research entity that exemplifies fundamentals of the NCATS mission:

- *Collaboration*: Multidisciplinary scientists from 260 institutions work together to conduct multisite studies, of which 91 are currently active and enrolling patients.

[1429] https://ncats.nih.gov/pubs/features/lam-treatment-sirolimus-fda-approved.
[1430] Langendonk JG, et al. *N Engl J Med* 2015;373(1):48-59. PMID: 26132941.
[1431] Shapiro AJ, et al. *Pediatr Pulmonol* 2016;51(2):115-32. PMID: 26418604.

- *Patient and community engagement*: More than 140 patient advocacy groups have partnered with consortia to assist in patient recruitment, study design, information dissemination and young scientist training.

- *Training*: Young scientists receive mentoring and guidance in conducting research on rare diseases.

- *Central data collection and storage*: The RDCRN DMCC provides the resources to pool data from RDCRN studies in a single location so that researchers can access information more easily and find links among diseases.

Autism Centers of Excellence

Establishment of the Autism Centers of Excellence

According to the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, about 1 in 68 8-year-old children has autism spectrum disorder (ASD).[1432] These estimates are based on data collected from health and special education records of children living in 11 areas of the U.S. during 2012. NIH is working to better understand the causes of ASD and to develop treatments for this serious and disabling disorder.

To address this public health challenge, Congress passed the *Combating Autism Act of 2006*, which emphasized the need to expand research and improve coordination among NIH Centers of Excellence focused on ASD. In response to the *Combating Autism Act*, the NIH Autism Coordinating Committee (ACC) formed the Autism Centers of Excellence (ACE) program by consolidating two previous ASD research programs—the Collaborative Programs of Excellence in Autism (CPEA, established in 1997) and Studies to Advance Autism Research and Treatment (STAART, established in 2002 and completed in 2008)—into a single research effort. The 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, focuses 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.

How the Autism Centers of Excellence Function Within the NIH Framework

The goals of the ACE program were established by the NIH ACC, a working group composed of the seven NIH ICs (NIMH, NICHD, NIDCD, NIEHS, NINDS, NINR, and NCCIH) that support ASD research and are tasked with enhancing the quality, pace, and coordination of research efforts at NIH. Five of the ACC ICs (NIMH, NICHD, NIDCD, NIEHS, and NINDS) provide funding to the ACE program and share administrative and oversight responsibilities.

The ACE program specifically solicits and funds research activities that address priority areas identified by the Strategic Plan for ASD Research developed by the Interagency Autism Coordinating Committee (IACC), a federal advisory committee established under the *Children's Health Act* and reauthorized under the *Combating Autism Act of 2006* and, most recently, under the *Autism Collaboration, Accountability, Research, Education, and Support (CARES) Act of 2014*. The IACC Strategic Plan for ASD Research serves as the roadmap for Federal ASD research. Research plan priority areas addressed through the ACE

[1432] Autism and Developmental Disabilities Monitoring Network (CDC). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, U.S., 2012. *MMWR* Surveillance Summaries. April, 2016 / 65(3);1-23. http://www.cdc.gov/mmwr/volumes/65/ss/ss6503a1.htm.

program include research on biomarkers, genetic susceptibility, pharmacological treatments, early intervention, and risk and protective factors.

The ACE program comprises several 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.

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."[1433] 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.

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, and/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.[1434, 1435] The estimated costs over a lifetime for each person can total $1.4 million to $3 million.[1436, 1437] Families often incur large debts for medical and education

[1433] Kanner L. *Nerv Child* 1943;2:217–50.
[1434] Ganz ML. *Arch Pediatr Adolesc Med.* 2007;161(4):343-9. PMID: 17404130.
[1435] Buescher AV, et al. *JAMA Pediatr* 2014;168(8):721-8. PMID: 24911948.
[1436] Ganz ML. *Arch Pediatr Adolesc Med* 2007;161(4):343-9. PMID: 17404130.
[1437] Buescher AV, et al. *JAMA Pediatr* 2014;168(8):721-8. PMID: 24911948.

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 68 children has ASD. Boys are approximately five times as likely as girls to have ASD.[1438] 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, 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.

To support and accelerate research in the causes, diagnosis, and treatment of ASD, NIH created NDAR, an informatics system and central data repository. The database collects a wide range of 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.

While 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 also coordinates data access with other Federal databases, such as the NIH Pediatric MRI Data Repository and the NIMH Repository and Genomics Resource. The NIMH repository is a national resource for researchers who study the genetics of complex mental disorders, including ASD, and stores human DNA, cell cultures, and clinical data.

NIH Funding for FY 2014 and FY 2015

Five NIH Institutes fund the ACE program: NICHD, NIDCD, NIEHS, NIMH, and NINDS. NIH funding for the ACE program, which includes three research centers (P50s), three cooperative agreements (U01s), and five research projects (R01 Networks), was $25.80 million in FY 2014 and $23.22 million in FY 2015.

[1438] https://www.cdc.gov/mmwr/volumes/65/ss/ss6503a1.htm

Programmatic and Research Activities and Outcomes

The activities and accomplishments of the ACE program—including those centers and networks that received support in the first round of funding (FY 2007) and those that were funded in the second round (FY 2012-)—are highlighted briefly below (see also Table 5).

Centers and Networks Funded in the First Round of the ACE Program (FY 2007)

- *Yale University.* Researchers are searching for biomarkers of visual engagement and auditory perception in infants at risk for ASD. A recent study from Emory University and 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. Another investigation found 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.[1439]

- *University of Illinois at Chicago.* Researchers are studying genetic factors, as well as brain chemicals and brain functions, which could account for repetitive behaviors in people with ASD. The researchers are also testing whether genetic differences influence how individuals respond to certain medications intended to reduce the frequency of these behaviors.

- *University of Washington.* Researchers are investigating 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 center 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.[1440]

- *University of North Carolina at Chapel Hill.* Investigators 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. A 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.[1441]

- *University of California, San Diego.* Building on earlier breakthrough studies linking brain development to the risk of autism, ACE investigators at UCSD recently 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

[1439] Shultz S, et al. *Proc Natl Acad Sci USA* 2011;108(52):21270-5. PMID: 22160686.
[1440] Faja S, et al. *J Autism Dev Disord* 2012;42(2):278-93. PMID: 21484517.
[1441] Kim JE, et al. *Arch Gen Psychiatry* 2010;67(11):1187-97. PMID: 21041620.

in the prefrontal cortex provide more precise targets for researchers to examine potential causes and treatments for ASD.[1442]

- *University of Pittsburgh.* The University of Pittsburgh ACE is studying how people with ASD learn and understand information.

- *Drexel University.* Researchers with the Drexel University network are studying possible risk factors and biological indicators of ASD before and soon after birth. This project is part of the Early Autism Risk Longitudinal Investigation.

- *University of California, Davis.* Recent 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.[1443] 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.[1444]

- *Wayne State University.* Investigators with the Wayne State network sites have completed enrollment for 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. A pilot study by the Wayne State researchers showed that buspirone improves social interaction and reduces repetitive behaviors, sensory dysfunction (extreme sensitivity or lack of sensitivity to light, noise, and touch), and anxiety in children with autism.

- *University of California, Los Angeles.* In the first of two ACE networks at UCLA, researchers are studying the causes of and treatments for social communication problems in people with ASD. These researchers will compare two types of intensive daily instruction for children with ASD who use only minimal verbal communication. These researchers plan to enroll 200 children in four cities: Los Angeles, Nashville, New York City, and Rochester, New York. Scientists hope this translational research will identify new intervention mechanisms for nonverbal children with autism.

- *University of California, Los Angeles.* In this second ACE network at UCLA, researchers have been utilizing large genomic databases to investigate how rare genetic variations, mutations, and abnormalities affect an individual's risk for autism. Their recent findings show that while common variations in genetic mutation at the individual level contribute less to a person's risk

[1442] Stoner R, et al. *N Engl J Med* 2014;370(13):1209-19. PMID: 24670167.
[1443] Rogers SJ, et al. *J Am Acad Child Adolesc Psychiatry.* 2012;51(10):1052-65. PMID: 23021480.
[1444] Estes A, et al. *J Autism Dev Disord* 2014;44(2):353-65. PMID: 23838727.

for autism,[1445] common inherited variants or mutations at the family level exert stronger effects on ASD risk.[1446]

Centers and Networks Funded in the Second Round of the ACE Program (FY 2012)

- *University of California, Los Angeles.* ACE investigators at the UCLA center will use brain imaging technology to chart brain development among individuals having gene variants suspected of contributing to ASD. The researchers hope to link genetic variants to distinct patterns of brain development, structure, and function in ASD. This ACE center is also examining the development of treatments to improve social behavior and attention in infants and acquisition of language among older children with ASD.

- *Emory University.* The team of researchers at the Emory ACE center will investigate risk and resilience in ASD, with particular interest in factors that lead to positive outcomes or social disability. The team will also conduct randomized clinical trials to develop treatments for 12-month-old children. Other projects include studies of model systems to chart brain development of neural networks involved in social interaction and longitudinal studies of how ASD unfolds across early development.

- *Boston University.* Researchers at this ACE center are investigating ASD in children with limited speech and will use 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 will also test new approaches to help young children with ASD acquire language.

- *University of California, Los Angeles.* The first of two UCLA networks will focus 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. The study will enroll 192 children (ages 5 to 8) across four sites (Los Angeles, Nashville, New York City, and Rochester, New York).

- *University of California, Los Angeles.* The second UCLA ACE network will build on its earlier work identifying genetic variants associated with a high risk developing autism, with an important new emphasis on recruiting at least 600 African American families with a child with ASD. This network will look for gene variants associated with autism in Americans with self-reported African ancestry and will test genetic risk factors identified in White populations to see what role those gene variants may play in autism in people of African descent.

- *Yale University.* An ACE network led by Yale University will investigate 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 and will focus on genes, brain function, and behavior throughout

[1445] Anney R, et al. *Hum Mol Genet* 2012;21(21):4781-92. PMID: 22843504.
[1446] Gaugler T, et al. *Nat Genet* 2014;46(8):881-5. PMID: 25038753.

childhood and adolescence. The objectives are to identify causes of ASD and develop new treatments. Additional sites in the network will include UCLA, Harvard, and the University of Washington.

- *University of North Carolina at Chapel Hill.* Continuing its efforts as an ACE network, the University of North Carolina–based program will conduct longitudinal brain imaging of a combined sample of 600 infants who are at high risk for later developing autism by virtue of having an older sibling with autism. The team's plan to gather more frequent scans until the children reach age 2 will allow investigators to gain a greater understanding of early brain development in children with ASD.

- *University of North Carolina at Chapel Hill.* The second ACE network at the University of North Carolina will test whether treatments with oxytocin nasal spray can improve social interaction and communication in children with ASD. Oxytocin is a neuropeptide used by brain cells to communicate and has been associated with social behaviors. The researchers plan to enroll 300 children (ages 3 to 17) with ASD from Boston; Chapel Hill and Durham, North Carolina; Nashville; New York City; and Seattle.

- *Mount Sinai School of Medicine.* These ACE network investigators will conduct a critical study to understand how genetic and environmental factors influence the development of autism. The team of American and international researchers will analyze detailed records and biospecimens from 4.5 million births involving 20,000 cases of ASD from 7 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.

- *Harvard Medical School.* This network will recruit patients with tuberous sclerosis complex (TSC), a rare genetic disease that causes tumors in the brain and other vital organs.[1447] Patients with TSC have an increased risk for developing autism. The researchers will track brain development in infants diagnosed with TSC to gain insights into how autism develops.

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, with membership comprising Planning and Evaluation Officers at the five NIH Institutes (NIMH, NICHD, NINDS, NIEHS, and NIDCD) that provide financial support and scientific expertise to the ACE program.

[1447] http://www.ninds.nih.gov/disorders/tuberous_sclerosis/tuberous_sclerosis.htm.

Between 2013 and2015, the AEIO working group continued gathering 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, was 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. Since the initial process evaluation, data from this program has been shared with the research community through NDAR and other accessible databases.

Future Directions

As in prior years, the NIH ACC convened an annual, two-day meeting where investigators present progress toward the goals of their ACE and exchanged ideas for collaborations. Some sessions addressed data-sharing options through NDAR, with time allotted for a question-and-answer period with NDAR staff. ACE principal investigators and project principal investigators, as well as core directors and data managers, attended the meeting. Principal investigators were encouraged to invite K award (career development grant) recipients, fellows, and postdoctoral students from their laboratories.

Table 5. Autism Centers of Excellence (ACEs).

Institution and Location	Year Started	
	First Round	Second Round
University of California, Davis, CA	2007	2013
University of California, Los Angeles, CA (1)	2007	2012
University of California, Los Angeles, CA (2)	2008	2013
University of California, Los Angeles, CA (3)	—	2012
University of California, San Diego, CA	2007	—
University of Illinois, Chicago, IL	2007	—
University of North Carolina, Chapel Hill, NC (1)	2007	2012
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

Institution and Location	Year Started	
	First Round	Second Round
Wayne State University, Detroit, MI	2008	—
Drexel University, Philadelphia, PA	2008	—
Boston University, Boston, MA	—	2012
Emory University, Atlanta, GA	—	2012
Harvard Medical School, Cincinnati Children's Hospital, and University of Cincinnati, Boston, MA and Cincinnati, OH	—	2012
Mount Sinai School of Medicine, New York City, NY	—	2012

Appendix A:
Legal Mandate for the Biennial Report

PUBLIC HEALTH SERVICE ACT

APPOINTMENT AND AUTHORITY OF DIRECTOR OF NIH (relevant excerpt)
SEC. 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; and

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BIENNIAL REPORTS OF DIRECTOR OF NIH
SEC. 403
(a) IN GENERAL.—The Director of NIH shall submit to the Congress on a biennial 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) Classification and justification for the priorities established by the agencies, including a strategic plan and recommendations for future research initiatives to be carried out under section 402(b)(7) through the Division of Program Coordination, Planning, and Strategic Initiatives.
(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 and other variables 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 and such other information as may be necessary to demonstrate compliance with section 492B (regarding inclusion of women and minorities in clinical research).

(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 promoting coordination of information among the centers of excellence.
(C) Recommendations for improving the effectiveness, efficiency, and outcomes of the centers of excellence.
(D) If no additional centers of excellence have been funded under this title since the previous report under this section, an explanation of the reasons for not funding any additional centers.

(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 (relevant excerpt)

SEC. 417G

(d) REPORTING.—

(1) BIENNIAL REPORTS.—The Director of NIH shall ensure each biennial 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 (relevant excerpts)

SEC. 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.

SEC. 486B BIENNIAL REPORT

(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 Offices) 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 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 (relevant excerpt)
SEC. 492B
(f) REPORTS BY ADVISORY COUNCILS.—The advisory council of each national research institute shall prepare biennial 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 biennial report under section 403.

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HUNTER KELLY NEWBORN SCREENING RESEARCH PROGRAM (relevant excerpt)
SEC. 1116
(c) REPORTS.—The Director is encouraged to include information about the activities carried out under this section in the biennial 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 (relevant excerpt)
SEC. 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.

UNITED STATES CODE

42 USC 284 note:
SEC. 106 of P.L. 109-482, NATIONAL INSTITUTES OF HEALTH REFORM ACT OF 2006
ENHANCING THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD (relevant excerpt)
(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

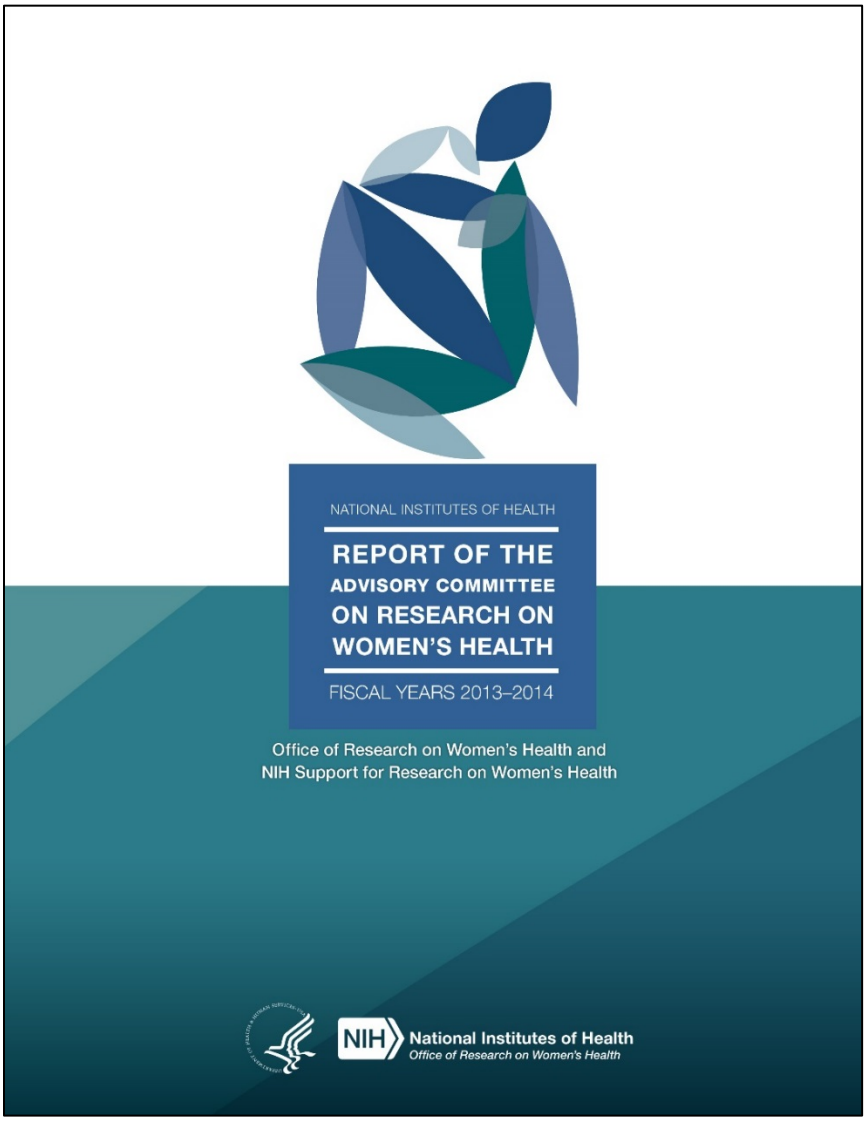
(2) otherwise securing institutional independence of pediatric clinical research centers with respect to finances, infrastructure, resources, and research agenda.

(b) REPORT.—As part of the biennial 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).

Appendix B:
Report of the Advisory Committee on Research on Women's Health

For the full report, please see:

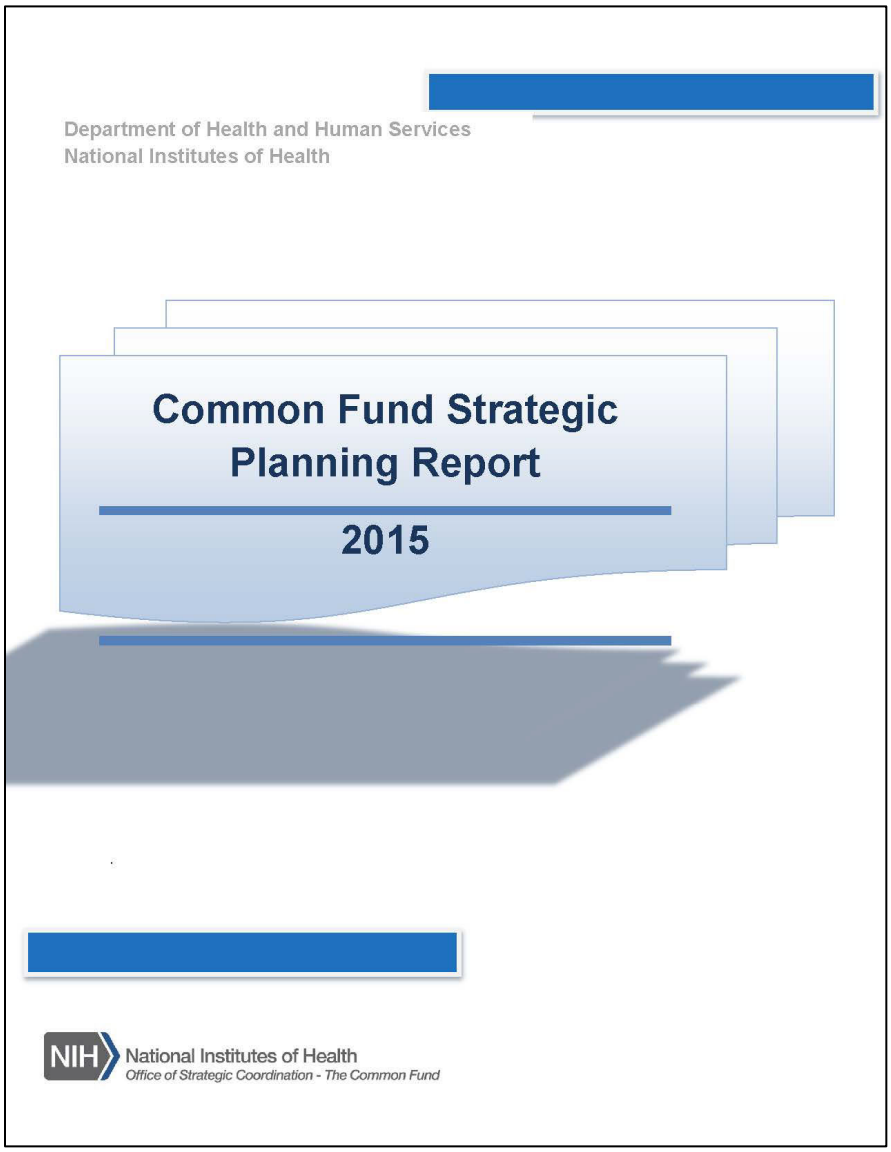
https://orwh.od.nih.gov/research/reports/



Appendix C:
Common Fund Strategic Planning Report, 2015

For the full report, please see:

https://commonfund.nih.gov/sites/default/files/2015%20Common%20Fund%20Strategic%20Planning%20Report_final%20-%20508.pdf



Appendix D:
Priorities and Plans of the ICs and Program Offices in the Office of the Director

This appendix provides links to the current mission statements and strategic plans of the NIH Institutes and Centers (ICs) and the program offices in the Office of the Director. The mission statements and strategic plans presented here classify and justify NIH priorities.

Institute Mission Statements

- National Cancer Institute (NCI): http://www.cancer.gov/aboutnci/overview/mission
- National Eye Institute (NEI): https://nei.nih.gov/about
- National Heart, Lung, and Blood Institute (NHLBI): https://www.nhlbi.nih.gov/about
- National Human Genome Research Institute (NHGRI): http://www.genome.gov/27534788
- National Institute on Aging (NIA): http://www.nia.nih.gov/about/mission
- National Institute on Alcohol Abuse and Alcoholism (NIAAA): http://www.niaaa.nih.gov/about-niaaa
- National Institute of Allergy and Infectious Diseases (NIAID): http://www.nih.gov/about/almanac/organization/NIAID.htm
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): http://www.niams.nih.gov/About_Us/Mission_and_Purpose/mission.asp
- National Institute of Biomedical Imaging and Bioengineering (NIBIB): http://www.nibib.nih.gov/About/MissionHistory
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): https://www.nichd.nih.gov/about/overview/mission/Pages/index.aspx
- National Institute on Deafness and Other Communication Disorders (NIDCD): http://www.nidcd.nih.gov/about/learn/pages/mission.aspx
- National Institute of Dental and Craniofacial Research (NIDCR): http://www.nidcr.nih.gov/AboutUs/MissionandStrategicPlan/MissionStatement/

- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): http://www.nih.gov/about/almanac/organization/NIDDK.htm
- National Institute on Drug Abuse (NIDA): http://www.drugabuse.gov/about-nida
- National Institute of Environmental Health Sciences (NIEHS): http://www.niehs.nih.gov/about/index.cfm
- National Institute of General Medical Sciences (NIGMS): https://www.nigms.nih.gov/About/Overview/Pages/default.aspx
- National Institute of Mental Health (NIMH): http://www.nimh.nih.gov/about/index.shtml
- National Institute on Minority Health and Health Disparities (NIMHD): http://nimhd.nih.gov/about/visionMission.html
- National Institute of Neurological Disorders and Stroke (NINDS): http://www.ninds.nih.gov/about-ninds/who-we-are/mission
- National Institute of Nursing Research (NINR): http://www.ninr.nih.gov/AboutNINR/NINRMissionandStrategicPlan/
- National Library of Medicine (NLM): http://www.nlm.nih.gov/about/index.html

Center Mission Statements

- Center for Information Technology (CIT): http://www.nih.gov/about/almanac/organization/CIT.htm
- Center for Scientific Review (CSR): http://public.csr.nih.gov/aboutcsr/Pages/default.aspx
- John E. Fogarty International Center (FIC): http://www.fic.nih.gov/About/Pages/mission-vision.aspx
- National Center for Advancing Translational Sciences (NCATS): http://www.ncats.nih.gov/about/center
- National Center for Complementary and Integrative Health (NCCIH)[1448]: https://nccih.nih.gov/about/ataglance

[1448] On December 16, 2014, President Barack Obama signed the Consolidated and Further Continuing Appropriations Act, 2015, which changed the name of NCCAM to the National Center for Complementary and Integrative Health (NCCIH). The change was made to more accurately reflect the Center's research commitment to studying promising health approaches that are already in use by the American public. The mission of NCCIH will remains unchanged.

- NIH Clinical Center (CC): http://clinicalcenter.nih.gov/about/welcome/mission.shtml

Office of the Director Mission Statements

- Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI): http://dpcpsi.nih.gov/about.aspx
- Office of Extramural Research (OER): http://grants.nih.gov/grants/intro2oer.htm
- Office of Intramural Research (OIR): https://oir.nih.gov/about
- Office of Management: http://om.od.nih.gov/vision.html
- Office of Science Policy: https://osp.od.nih.gov/about-us/
- Office of Communications and Public Liaison: https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison
- Office of Equity, Diversity and Inclusion: https://www.edi.nih.gov/
- Office of Legislative Policy and Analysis: https://www.nih.gov/olpa/olpa-mission
- Office of Ombudsman/Center for Cooperative Resolution: https://ombudsman.nih.gov/about_us
- NIH Ethics Office: http://ethics.od.nih.gov/overview.htm
- Office of the Chief Information Officer: https://ocio.nih.gov/aboutus/Pages/default.aspx

Institute and Center Strategic Plans

- The full listing is available at https://report.nih.gov/strategicplans/.

Appendix E:
Research Training and Graduate Medical Education Data

NRSA and NLM Research Training Programs: Ph.D. Recipients by Field of Study[1449]

Field of Study	Year of Ph.D.	
	2014	2015
Life Sciences	**2,481**	**2,496**
Biological/Biomedical Sciences	2,294	2,286
Bacteriology	2	4
Biochemistry	180	153
Bioinformatics	35	39
Biology/Biomedical Sciences, General	43	37
Biology/Biomedical Sciences, Other	12	17
Biomedical Sciences	100	102
Biometrics and Biostatistics	35	28
Biophysics	61	69
Biotechnology	7	3
Botany/Plant Biology	2	2
Cancer Biology	119	132
Cell/Cellular Biology and Histology	104	99
Computational Biology	35	25
Developmental Biology/Embryology	66	62
Ecology	4	8
Endocrinology	10	6
Entomology	2	3
Environmental Toxicology	9	5
Epidemiology	58	82
Evolutionary Biology	13	16
Genetics/Genomics, Human and Animal	149	128
Immunology	196	213
Marine Biology and Biological Oceanography	3	1
Microbiology	116	113
Molecular Biology	190	179
Neurosciences and Neurobiology	410	440
Nutritional Sciences	19	21
Parasitology	8	9
Pathology, Human and Animal	39	29
Pharmacology, Human and Animal	98	90

[1449] Source: Data were drawn from the NIH Trainee and Fellow File, IMPAC II, and the Doctorate Records File on July 22, 2015, and are subject to change. CTSA trainees are included in the NRSA data provided.

Field of Study	Year of Ph.D.	
	2014	2015
Physiology, Human and Animal	49	54
Plant Genetics	4	7
Structural Biology	19	16
Toxicology	33	34
Virology	64	57
Wildlife Biology	0	1
Zoology	0	2
Health Sciences	180	207
Environmental Health	6	13
Gerontology	1	3
Health and Behavior	3	13
Health Policy Analysis	2	7
Health Sciences, General	0	2
Health Sciences, Other	16	9
Health Systems/Services Administration	6	1
Kinesiology/Exercise Physiology	3	8
Nursing Science	52	47
Oral Biology/Oral Pathology	3	8
Pharmaceutical Sciences	16	21
Public Health	47	49
Rehabilitation/Therapeutic Services	8	7
Speech-Language Pathology and Audiology	16	15
Veterinary Sciences	1	4
Agricultural Sciences/Natural Resources	7	3
Animal Nutrition	1	1
Environmental Science	4	1
Food Science	1	0
Natural Resource/Environmental Economics	0	1
Plant Sciences, Other	1	0
Psychology	**165**	**155**
Clinical Psychology	56	80
Cognitive Psychology and Psycholinguistics	21	19
Counseling	1	1
Developmental and Child Psychology	17	12
Experimental Psychology	9	14
Health and Medical Psychology	9	4
Human Development and Family Studies	3	0
Neuropsychology/Physiological Psychology	19	10
Personality Psychology	2	1
Psychology, General	8	8
Psychology, Other	7	2
Psychometrics and Quantitative Psychology	2	1
School Psychology	1	1
Social Psychology	10	2
Social Sciences	**59**	**67**
Anthropology, Cultural	5	6

Field of Study	Year of Ph.D.	
	2014	2015
Demography/Population Studies	6	10
Economics	11	13
Geography	0	1
Gerontology	0	2
Linguistics	1	5
Political Science and Government	0	1
Public Policy Analysis	4	6
Social Sciences, Other	1	1
Sociology	29	21
Statistics	1	1
Urban/City, Community and Regional Planning	1	0
Physical Sciences	**150**	**138**
Atmospheric Science and Meteorology	1	0
Chemistry	74	75
Analytical Chemistry	6	9
Chemistry, General	10	6
Chemistry, Other	20	16
Inorganic Chemistry	5	7
Medicinal Chemistry	7	9
Organic Chemistry	19	19
Physical Chemistry	6	6
Theoretical Chemistry	1	3
Ocean/Marine Sciences	1	0
Physics	40	34
Applied Physics	1	4
Atomic/Molecular/Chemical Physics	0	1
Biophysics	17	10
Condensed Matter/Low Temperature Physics	1	1
Medical Physics/Radiological Science	14	10
Nuclear Physics	1	0
Optics/Photonics	4	5
Physics, General	2	3
Mathematics	**23**	**18**
Applied Mathematics	3	1
Mathematics/Statistics, General	2	2
Mathematics/Statistics, Other	2	2
Statistics	16	13
Computer Sciences	**12**	**11**
Computer Science	11	7
Computer and Information Sciences, General	0	2
Computer and Information Sciences, Other	0	1
Information Science and Systems	1	1
Engineering	**217**	**233**
Aerospace, Aeronautical and Astronautical Engineering	1	0
Bioengineering and Biomedical Engineering	174	195
Chemical Engineering	17	20

Field of Study	Year of Ph.D.	
	2014	2015
Civil Engineering	0	1
Computer Engineering	2	1
Electrical, Electronics, and Communications Engineering	6	5
Engineering Mechanics	0	1
Engineering Science	1	0
Engineering, Other	3	0
Environmental/Environmental Health Engineering	4	1
Industrial and Manufacturing Engineering	1	0
Materials Science Engineering	5	4
Mechanical Engineering	1	3
Polymer and Plastics Engineering	0	1
Systems Engineering	1	1
Transportation and Highway Engineering	1	0
Education	**9**	**3**
Humanities	**1**	**3**
Other Fields	**13**	**12**
Total	**3,095**	**3,107**

Demographic Characteristics of NRSA Participants[1450]

Demographic Characteristic	FY 2014	FY 2015
Gender		
Female	52.4%	51.9%
Male	45.1%	44.8%
Unknown	2.3%	3.3%
Withheld	0.2%	0.0%
Race		
White	65.8%	65.3%
Asian	15.0%	15.0%
African American	6.4%	6.1%
Native American	0.6%	0.5%
Native Hawaiian/Pacific Islander	0.2%	0.2%
Multiple Races (including more than 1 race)	3.9%	4.1%
Withheld	7.9%	8.6%
Unknown	0.2%	0.2%
Ethnicity		
Hispanic	10.5%	10.2%
Non-Hispanic	84.2%	84.0%
Unknown	0.3%	0.2%
Withheld	5.1%	5.7%

[1450] The NRSA training grants are T32, T34, T35, T90, TL1, and TU2. The fellowship grants are F30, F31, F32, and F33. Data were drawn from IMPAC II current files and the Doctorate Records File on July 22, 2016, and are subject to change. For individuals whose race or ethnicity was unknown or withheld, IMPAC II data were supplemented with information from the Doctorate Records File. CTSA trainees are included in the NRSA data provided.

Successfully Completed Residency and Subspecialty Training by Academic Year

NIH Clinical Center Program Specialty	Completed	
	2013/2014	2014/2015
Allergy and Immunology	3	4
Medical Genetics	3	4
Medical Biochemical Genetics	0	3
Critical Care Medicine	5	3
Endocrinology, Diabetes, and Metabolism	4	6
Hematology	4	4
Infectious Disease	4	3
Oncology	10	10
Rheumatology	3	3
Pathology—Anatomic and Clinical	3	3
Blood Banking/Transfusion Medicine	2	2
Cytopathology	1	1
Hematology (Pathology)	2	2
Pediatric Endocrinology	2	2
Psychiatry	0	1
Vascular Neurology	4	3
Hospice and Palliative Medicine	1	2
Neurological Surgery (new program)	0	0
Total	51	56

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 fiscal year 1994. These reports are one component of NIH's policy on the Inclusion of Women and Minorities as Subjects in Clinical Research.

Biennial reports on inclusion are produced with all NIH enrollment information and for each NIH Institute and Center that supports clinical research. For links to the NIH-wide report, as well as each IC report, please see https://report.nih.gov/recovery/inclusion_research.aspx.

Please note that the most recent NIH-wide report, *FISCAL YEARS 2013 & 2014 Trans-NIH Report on Inclusion of Women and Minorities in Clinical Research*, is published as Section IV (starting on page 37) of the *Report of the Office of Research on Women's Health*.

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
A New Generation Clinical Decision Support System	NLM	NLM	University of Pittsburgh at Pittsburgh
A Novel Informatics Approach to Understanding Complex Muscle Fiber Phenotypes	NLM	NLM	Brigham and Women's Hospital
A Platform for Modeling the Global Impact of Climate Change on Infectious Disease	NLM	NLM	Children's Hospital Corporation
A Prospective, Randomized, Clinical Trial to Evaluate Two Novel Therapies, Mycoph	NIAAA	NIAAA	Southern California Institute for Research and Education
A Unified Clinical Genomics Database	NHGRI	NHGRI and NICHD	Brigham and Women's Hospital
Accelerating Medicines Partnership (AMP) Type 2 Diabetes Knowledge Portal	NIDDK	NIDDK	Eli and Edythe L. Broad Institute of MIT and Harvard
Action for Health in Diabetes (Look AHEAD) and Follow-Up Study	NIDDK	NIDDK, NHLBI, and ORWH	Multiple (Wake Forest School of Medicine, Data Coordinating Center (DCC)
Active Patient Participation in a Disease Registry for Comparative Effectiveness	NLM	NLM	Children's Hospital Corporation
Acute Liver Failure Registry in the Adult Acute Liver Failure Study Group (ALFSG)	NIDDK	NIDDK	Multiple (University of Texas Southwestern Medical Center, DCC)

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
AFINITI—An Augmented System for Neuroimaging Followup	NLM	NLM	Methodist Hospital Research Institute
AIDSinfo/infoSIDA	NLM	NLM, NIAID, and OD/OAR	NLM
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
Alu Pairs Database	NIEHS	NIEHS and NLM	Genetic Information Research Institute
Alzheimer's Disease Neuroimaging Initiative (ADNI)	NIA	NIA, NIMH, NINDS, and 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
American Indian Health	NLM	NLM	NLM
American Time Use Survey Well-Being Module	NIA	NIA	Bureau of Labor Statistics
An Open Source Digital Pathology System Supporting Multi-Touch Interaction	NIBIB	NIBIB	Kitware
AphasiaBank: A Shared Database for the Study of Aphasic Communication	NIDCD	NIDCD	Carnegie Mellon University
Asian American Health	NLM		
Asia-Pacific HIV Research Collaboration	NIAID	NLM	NLM
Aspergillus Genome Database	NIAID	NIAID, NCI, and NICHD	Foundation for AIDS Research

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Asthma Birth Cohorts Database	NIAID	NIAID,	Stanford University
Atlas of Mouse Liver Lesions	NIEHS/NTP	NIAID	NIAID
Audiological and Genetic Resource for Pediatric Hearing Research	NIDCD	NIEHS/NTP	NIEHS/NTP
Autism Genetic Resource Exchange (AGRE)	NIMH	NIDCD	Children's Hospital of Philadelphia
Belarus Tuberculosis Portal	NIAID	NIMH and NICHD	Autism Speaks
Beta Cell Biology Consortium (BCBC)	NIDDK	NIAID	NIAID
BETRNet Patient Registry-Virtual Biorepository	NCI	NIDDK	Multiple (Vanderbilt Medical Center, CC)
BioGRID: An Open Integrated Resource for Biological Interaction Data	OD/ORIP	NCI	Vanderbilt University
Biological Biochemical Image Database (BBID)	NIA	OD/ORIP	Mount Sinai Hospital, Samuel Lunenfeld Research Institute
Biological Magnetic Resonance Data Bank	NLM	NIA	NIA
Biological Specimen and Data Repositories Information Coordinating Center (BioLINCC)	NHLBI	NLM	University of Wisconsin Madison
Biomedical Informatics Research Network (BIRN) Data Repository		NHLBI	Information Management Services, Inc.
Biomedical Informatics Research Network (BIRN) Data Repository			University of California, San Diego
Biomedical Translational Research Information System (BTRIS)	CC		University of California, San Diego
BioSEND Biomarkers Repository	NINDS	CC	NIH Clinical Center
Biospecimen Research Database	NCI	NINDS	Indiana University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Blueprint Neurotherapeutics Database	NINDS	NCI	NCI
Bookshelf	NLM	NINDS	Collaborative Drug Discovery, Inc.
Boston Area Community Health (BACH) III Survey	NIDDK	NLM	NLM
Breast and Colon Cancer Family Registries	NCI	NIDDK	New England Research Institutes, Inc.
Breast Cancer Information Core (BIC)	NHGRI	NCI	Multiple
Breast Cancer Surveillance Consortium	NCI	NHGRI	NHGRI
Bridges to Health Information for Individuals with Serious Mental Illness	NLM	NCI	Multiple
CADD Group Chemoinformatics Tools and User Services	NCI	NLM	University of Massachusetts Medical School–Worchester
caIntegrator	NCI	NCI	NCI
Cancer Control P.L.A.N.E.T.	NCI	NCI	NCI
Cancer Data Access System (CDCAS) for PLCO, NLST and IDATA Studies	NCI	NCI	NCI
Cancer Genome Anatomy Project (CGAP)	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

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Cancer Research Network	NCI	NCI	NCI
Cancer Survivor Prevalence Data	NCI	NCI	NCI
Cancer Therapy Evaluation Program Enterprise (CTEP-ESYS)	NCI	NCI	NCI
Cancer Trends Progress Report	NCI	NCI	NCI
Carcinogenic Potency Database (CPDB)	NLM	NCI	NCI
Cardiovascular Research Grid (CVRG)	NHLBI	NLM	NLM and University of California, Berkeley Lawrence Berkeley National Laboratory
Catalog of microRNA eQTLs	NHLBI	NHLBI	Johns Hopkins University
CCASAnet: Caribbean, Central and South America Network for HIV Epidemiology	NIAID	NHLBI and NLM	NHLBI
Cell Image Library	NIGMS	NIAID	Vanderbilt University School of Medicine
CellMiner	NCI	NIGMS	University of California, San Diego
Center for International Blood and Marrow Transplant Research (CIBMTR)	NCI	NCI	NCI
Center for Molecular Microscopy	NCI	NCI, NHLBI, and NIAID	Medical College of Wisconsin and National Marrow Donor Program
Center for Research in Reproduction Ligand Assay and Analysis Core	NICHD	NCI	NCI
Center for Zebrafish Chromatin and Epigenetics	NICHD	NICHD	University of Virginia

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Central Africa International Epidemiologic Databases to Evaluate AIDS (IEDEA)	NIAID	NICHD	University of Utah
Chemical Carcinogenesis Research Information System (CCRIS)	NLM	NIAID, NCI, and NICHD	RTI International
Chemical Effects in Biological Systems	NIEHS	NLM	NLM
Chemical Hazards Emergency Medical Management (CHEMM)	NLM	NIEHS	NIEHS
ChemIDplus	NLM	NLM	NLM
Chest X-Ray Image Dataset	NLM	NLM	NLM
Childhood Liver Disease Research Network	NIDDK	NLM	Indiana University
China Health and Retirement Longitudinal Study	NIA	NIDDK	Multiple (University of Michigan, DCC)
Chronic Kidney Disease in Children (CKiD) Study	NIDDK	NIA	Peking University
Chronic Renal Insufficiency Cohort (CRIC) Study	NIDDK	NIDDK, NICHD, and NHLBI	Multiple (Johns Hopkins University, DCC)
Cistrome	NCI	NIDDK	Multiple (University of Pennsylvania, DCC)
Classification of Laws Associated with School Students	NCI	NCI	Dana-Farber Cancer Institute
Clinical Research Study Investigators' Toolbox	NIA	NCI	NCI
Clinical Trial Reporting Program (CTRP)	NCI	NIA	NIA
Clinical Trials Dissemination Library	NIDA	NCI	Multiple
Clinical Trials Public Data Share Website	NIDA	NIDA	Washington University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Clinical Trials Support Unit Enterprise Systems (CTSU-ESYS)	NCI	NIDA	NIDA
ClinicalTrials.gov	NLM	NCI	NCI
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	NLM	NLM
Collaborative Health Outcomes Information Registry (CHOIR)	NIDA	NICHD	Emory University
Collaborative Initiative on Fetal Alcohol Spectrum Disorders—Informatics Core	NIAAA	NIDA, NIA, NINR, NEI, and NINDS	Stanford University School of Medicine
Collaborative Islet Transplant Registry (CITR)	NIDDK	NIAAA	Indiana University Bloomington
Collaborative Studies on Genetics of Alcoholism (COGA) Database	NIAAA	NIDDK	EMMES Corporation
Colorectal Cancer Mortality Projections	NCI	NIAAA	State University of New York Downstate Medical Center
COMBINE (Combining Medications and Behavioral Interventions) Data Set	NIAAA	NCI	NCI
Comparative Toxicogenomics Database (CTD)	NIEHS	NIAAA	NIAAA
Comprehensive Database of Drug Discrimination and Self-Administration Research	NIDA	NIEHS and NLM	Mount Desert Island Biological Laboratory
Computer Access to Research on Dietary Supplements (CARDS) Database	OD/ODS	NIDA	European Behavioural Pharmacology Society

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Connectome Coordination Facility	NIMH	OD/ODS	OD/ODS
Consensus Coding Sequence Regions (CCDS) Database	NLM	NIH Blueprint	Washington University
Conserved Domain Database (CDD)	NLM	NLM	NLM
Consortium on Interplay of Genes and Environment across Multiple Studies	NIA	NLM	NLM
Continued Development and Maintenance of ITK-SNAP 3D Image Segmentation Software	NIBIB	NIA	
Coordinating and Bioinformatics Unit for the DCC/MMPC (Diabetic Complications Consortium/ Mouse Metabolic Phenotyping Centers)	NIDDK	NIBIB	Univ. Penn
CPTAC Antibody Portal	NCI	NIDDK	Augusta University
CPTAC Assay Portal	NCI	NCI	Leidos
CPTAC Data Portal	NCI	NCI	Enterprise Science and Computing (ESAC), Inc.
CPTAC Huddle	NCI	NCI	ESAC, Inc.
CRCNS Data Sharing: Exchange and Evaluation of Reduced Neuron Models	NIBIB	NCI	Huddle
CRCNS US-German Data Sharing Proposal: Analysis and Visualization of Neural Oscillations in Electrocorticographic Signals	NIBIB	NIBIB	Arizona State University–Tempe
CRCNS: Multi-Scale Estimators for Diffusion MRI of the Brain	NIBIB	NIBIB	New York University School of Medicine
Creating a Developmental Gene Expression Atlas for Rhesus Macaque Brain	NIMH	NIBIB	University of California, San Diego

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Critical Care Informatics	NIBIB	NINDS and NIMH	Allen Institute for Brain Science
CSER Coordinating Center	NHGRI	NIBIB	Massachusetts Institute of Technology
Cytogenetic Models Resource for Chromosomal Disorders	NICHD	NHGRI	University of Washington
DAIDS HIV/OI/TB Therapeutics Database	NIAID	NICHD	Jackson Laboratory
DailyMed	NLM	NIAID	Gryphon Scientific LLC
Data Archive and Specimen Hub (DASH)	NICHD	NLM	NLM
Data Management and Coordinating Center (DMCC)	NCATS	NICHD	NICHD
Data Structures, Algorithms and Tools for Ontological Discovery	NIAAA	NCATS	University of South Florida
Database for Annotation, Visualization, and Integrated Discovery (DAVID)	NIAID	NIAAA	Jackson Laboratory
Database of Expressed Sequence Tags (dbEST)	NLM	NIAID	NIAID
Database of Genome Survey Sequences (dbGSS)	NLM	NLM	NLM
Database of Genomic Structural Variation (dbVar)	NLM	NLM	NLM
Database of Genotypes and Phenotypes (dbGaP)	NLM	NLM	NLM
Database of Longitudinal Studies	NIA	NLM	NLM
Database of Major Histocompatibility Complex (dbMHC)	NLM	NIA	NIA

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Database of Short Genetic Variations (dbSNP)	NLM	NLM	NLM
Decision Support System for Temporal Lobe Epilepsy	NIBIB	NLM	NLM
Developing and Applying Information Extraction Resources and Technology to Create	NLM	NIBIB	Henry Ford Health System
Development and Evaluation of a Learning Electronic Medical Record System	NLM	NLM	University of Colorado Denver
Development of a Prototype Healthcare Intranet for Improved Health Outcomes	NIBIB	NLM	University of Pittsburgh at Pittsburgh
Development of an Infertility Family Registry (IFRR)	NICHD	NIBIB	Massachusetts General Hospital
Development of dictyBase, an Online Informatics Resource	NIGMS	NICHD	Dartmouth College
Developmental and Reproductive Toxicology Database (DART)	NLM	NIGMS	Northwestern University
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)	NIDDK	NLM	NLM
Diabetes Prevention Program Outcomes Study (DPPOS)	NIDDK	NIDDK	Multiple (NIDDK, DCC)
Diazeniumdiolate Database	NCI	NIDDK	Multiple (George Washington University, DCC)
Dietary Supplement Ingredients Database	OD/ODS	NCI	NCI
Dietary Supplement Label Database	NLM	OD/ODS	OD/ODS, FDA, and USDA
Digital Collections	NLM	ODS and NLM	ODS

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Disaster Lit: Resource Guide for Disaster Medicine and Public Health	NLM	NLM	NLM
Disaster Research Response (DR2) Data Collection Tools	NLM	NLM	NLM
Disorders of Sex Development Network Patient Registry	NICHD	NLM and NIEHS	NLM, NIEHS, CDC, Center for Research on the Epidemiology of Disasters (CRED), and NIOSH
Drug Information Portal	NLM	NICHD	UCLA
Drug-Induced Liver Injury Network (DILIN) Retrospective Study (ILIAD)	NIDDK	NLM	NLM
DrugMatrix	NIEHS/NTP	NIDDK	Multiple (Duke University, DCC)
DS-Connect™: The Down Syndrome Registry	NICHD	NIEHS/NTP	NIEHS/NTP
Early Detection Research Network (EDRN)	NCI	NICHD	NIH
East Africa IeDEA Regional Consortium	NIAID	NCI	Multiple
EM Open Connectome Project	NIBIB	NIAID, NCI, and NICHD	Indiana University
eMERGE Coordinating Center	NHGRI	NIBIB	Johns Hopkins University (subcontract to Harvard)
ENCODE Data Analysis Center: EDAC	NHGRI	NHGRI and OD	Vanderbilt University Medical Center
ENCODE Data Coordinating Center	NHGRI	NHGRI	University of Massachusetts Medical School–WorcesterNI
Endometrium Database Resource	NICHD	NHGRI	Stanford University
English Longitudinal Study of Ageing	NIA	NICHD	University of California, San Francisco
Environmental Polymorphisms Registry (EPR)	NIEHS	NIA	University College London

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)	OER	NIEHS	Integrated Laboratory Systems, Inc., and University of North Carolina
Eukaryotic Pathogen Database Resources (EuPathDB)	NIAID	OD	NIH
exRNA Research Portal	NIDA	NIAID	University of Pennsylvania
exRNA Virtual Repository	NIDA	OD/OSC (Common Fund)	Baylor University
FaceBase: A Resource for Craniofacial Researchers	NIDCR	OD/OSC (Common Fund)	Baylor College of Medicine
Finding Cancer Statistics	NCI	NIDCR	University of Southern California
FITBIR (Federal Interagency Traumatic Brain Injury Research) Informatics System	NINDS	NCI	NCI
FlyBase: A Drosophila Genomic and Genetic Database	NHGRI	NINDS and DoD	NIH CIT
Food Attitudes and Behavior Survey Project	NCI	NHGRI	Harvard University
Gabriella Miller Kids First Pediatric Research Program	NICHD and NCI	NCI	NCI
Gastroparesis Registry 2, Gastroparesis Clinical Research Consortium (GpCRC)	NIDDK	OD/OSC (Common Fund)	NIH
Gateway to Global Aging Data	NIA	NIDDK	Multiple (Johns Hopkins University, DCC)
Geisha, a Chicken Embryo Gene Expression Resource	NICHD	NIA	University of Southern California
GenBank	NLM	NICHD	University of Arizona
GENCODE: Comprehensive Gene Annotation for Human and Mouse	NHGRI	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Gene	NLM	NHGRI	Wellcome Sanger Institute
Gene Expression Database for Mouse Development	NICHD	NLM	NLM
GeneNetwork	NIAAA	NICHD	Jackson Laboratory
Genes and Disease	NLM	NIAAA	University of Tennessee Health Sciences Center
Genetic and Rare Diseases Information Center (GARD)	NCATS	NLM	NLM
Genetic Association Database	NIA, CIT	NHGRI	ICF International
Genetic Testing Registry (GTR)	NLM	NIA and CIT	NIH
Genetic Toxicology Databank (GENE-TOX)	NLM	NLM and OD	NLM
Genetics Home Reference	NLM	NLM	EPA
GenitoUrinary Development Molecular Anatomy Project (GUDMAP)	NIDDK	NLM	NLM
Genome	NLM	NIDDK	University of Southern Edinburgh
Genomic Database for *Candida albicans*	NIDCR	NLM	NLM
Genomic Database for the Yeast *Saccharomyces*	NHGRI	NIDCR	Stanford University
Genomic Datasets for Cancer Research	NCI	NHGRI	Stanford University
Genomics and Bioinformatics Software Tools	NCI	NCI	NCI
Genotype-Tissue Expression (GTEx) Portal	NHGRI	NCI	NCI

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
GEO (Gene Expression Omnibus)	NLM	OD/OSC (Common Fund)	Eli and Edythe L. Broad Institute of MIT and Harvard
Geographic Information System for Breast Cancer Studies on Long Island	NCI	NLM	NLM
Global Cancer Project Map	NCI	NCI	Multiple
Global Rare Diseases Registry Data Repository (GRDR^{R})	NCATS	NCI	Global Oncology, Inc.
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)	NIDDK	NCATS	NCATS
Glycomics/Legacy Informatics Resources for Glycomics	NIGMS	NIDDK	Multiple (George Washington University, DCC)
Graphics to Enhance Health Education Materials for Underrepresented Populations	NLM	NIGMS	Massachusetts Institute of Technology
Grid-Enabled Measures	NCI	NLM	University of Utah
H3ABioNet: A Sustainable African Bioinformatics Network for H3Africa	NHGRI	NCI	NCI
Harmonizome	NCI	OD/OSC (Common Fund)	University of Cape Town
Hazardous Substances Data Bank (HSDB)	NLM	OD/OSC (Common Fund)	Icahn School of Medicine at Mount Sinai
Haz-Map: Information on Hazardous Chemicals and Occupational Diseases	NLM	NLM	NLM
Health and Retirement Study	NIA	NLM	NLM
Health Disparities Calculator (HD*Calc)	NCI	NIA	University of Michigan
Health Hotlines	NLM	NCI	NCI

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Health Information National Trends Survey	NCI	NLM	NLM
Health Services and Sciences Research Resources Database (HSRR)	NLM	NCI	NCI
Health Services Research Projects in Progress (HSRProj) Database	NLM	NLM	NLM
Health Services/Technology Assessment Text (HSTAT)	NLM	NLM	NLM
HealthReach	NLM	NLM	NLM
HealthReach	NLM	NLM	NLM
Hemagglutinin Structure Prediction Server (HASP)	NIAID	NLM	NLM
Hepatitis B Research Network: Observational Databases in Adults and Children	NIDDK	NIAID	NIAID
Hereditary Causes of Nephrolithaisis and Kidney Failure	NIDDK	NIDDK	Multiple (University of Pittsburgh, DCC)
Histone Database	NHGRI	NIDDK	Mayo Clinic, Rochester
HIV Molecular Immunology Database	NIAID	NHGRI, and NLM	NHGRI and NLM
HIV Protein Interaction Database	NIAID	DOE and NIAID	Los Alamos National Laboratory
HIV Sequence Database	NIAID	NCBI and NIAID	DAIDS/NIAID and NCBI
HIV/AIDS Cancer Match Study	NCI	DOE and NIAID	Los Alamos National Laboratory
HIV-1 Resistance Mutation Database	NIAID	NCI	NCI
HIV-1, Human Interaction Database	NLM	DOE and NIAID	Los Alamos National Laboratory
HomoloGene	NLM	NIAID and NLM	NLM
Household Products Database	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Human "Brain Bank" Tissue for Alcohol Research	NIAAA	NLM	NLM
Human Biological Data Interchange	NIDDK	NIAAA	University of Sydney
Human DNA Polymerase Gamma Mutation Database	NIEHS	NIDDK	National Disease Research Interchange (NIDDK and others)
Human Epigenome Atlas	NIEHS, NIDA, and NIDOCD	NIEHS	NIEHS
Human Islet Research Network (HIRN)	NIDDK	OD/OSC (Common Fund)	Multiple; see http://www.roadmapepigenomics.org/participants
Human Microbiome Project Data Analysis and Coordination Center Data Portal	NHGRI	NIDDK	Multiple (Beckman Research Institute of City of Hope, Coordinating Center)
Human Nutrition Research and Information Management (HNRIM) Database	NIDDK	OD/OSC (Common Fund)	University of Maryland, Baltimore
Human Oral Microbiome Database (HOMD)	NIDCR	NIDDK	NIDDK
ICBP Data Portal	NCI	NIDCR	Forsyth Institute
IeDEA West Africa Collaboration	NIAID	NCI	Eli and Edythe L. Broad Institute of MIT and Harvard
IGNITE Network Administrative Coordinating Center	NHGRI	NIAID, NCI, and NICHD	Association for the Development of Teaching and Research at Universities (ADERA)
Images from the History of Medicine	NLM	NHGRI	University of Pennsylvania
ImmPort	NIAID	NLM	NLM
Immune Epitope Database and Analysis Program	NIAID	NIAID	Northrop Grumman Corporation

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Immune Polymorphism Database/Major Histocompatibility Complex of Non-Human Primates	NIAID	NIAID	La Jolla Institute for Allergy & Immunology
ImmuneSpace (Human Immunology Project Consortium (HIPC) Database)	NIAID	NIAID	European Molecular Biology Laboratory/European Bioinformatics Institute
Inferred Biomolecular Interactions Server (IBIS)	NLM	NIAID	Fred Hutchinson Cancer Research Center
Influenza Research Database	NIAID	NLM	NLM
Influenza Virus Resource	NLM	NIAID	Northrop Grumman Corporation and J. Craig Venter Institute
Informatics for Integrating Biology to the Bedside (i2b2)	NIMHD	NLM	NLM
Informatics for Integrative Brain Tumor Whole Slide Analysis	NLM	NIMHD	Morehouse School of Medicine
Inherited Bone Marrow Failure Syndromes	NCI	NLM	Emory University
InSPECt: Interactive Surveillance Portal for Evaluating Clinical Support	NLM	NCI	NCI
Instruments to Detect Cognitive Impairment in Older Adults	NIA	NLM	Tulane University of Louisiana
Integrated Risk Information System (IRIS)	NLM	NIA	NIA
Integrating Data, Models, and Reasoning in Critical Care	NIBIB	NLM, EPA	NLM
Integrative Analysis of Longitudinal Studies on Aging	NIA	NIBIB	Massachusetts Institute of Technology
Integrative Neuroscience Initiative on Alcoholism	NIAAA	NIA	Oregon Health Sciences University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Interagency Registry for Mechanically Assisted Circulatory Support	NHLBI	NIAAA	Scripps Research Institute
International Cancer Research Partnership	NCI	NHLBI	University of Alabama at Birmingham
International Epidemiologic Databases to Evaluate AIDS Southern Africa Collaboration (IeDEA-SA)	NIAID	NCI	NCI
International Myositis Assessment and Clinical Studies Group (IMACS) Outcomes Repository	NIEHS	NIAID, NCI, and NICHD	University of Bern
International Registry of Werner Syndrome	NCI	NIEHS	NIEHS
International Registry of Werner Syndrome	NIA	NCI and NIA	University of Washington
International Research Registry Network for Sjögren's Syndrome	NIDCR	NCI and NIA	University of Washington
International Skeletal Dysplasia Registry	NICHD	NIDCR	University of California, San Francisco
International Toxicity Estimates for Risk (ITER)	NLM	NICHD	Cedars-Sinai Medical Center
Irish Longitudinal Study on Aging	NIA	NLM	Toxicology Excellence for Risk Assessment
Japanese Study of Aging and Retirement	NIA	NIA	Trinity College, Dublin
Jackson Laboratories Neural Tube Defects Resource	NICHD	NIA	Research Institute of Economy, Trade, and Industry; Hitotsubashi University; and University of Tokyo
Korean Longitudinal Study of Aging	NIA	NICHD	Jackson Laboratory

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
LactMed (Drugs and Lactation Database)	NLM	NIA	Korea Labor Institute
Library of Integrated Network-Based Cellular Signatures (LINCS)	NHLBI and NHGRI	NLM	NLM
Li-Fraumeni Syndrome Study	NCI	OD/OSC (Common Fund)	Multiple
Limited Access Datasets from NIMH Clinical Trials	NIMH	NCI	NCI
LiverTox (Database of Clinical and Research Information on Drug-Induced Liver Injury)	NIDDK and NLM	NIMH	NIMH
Living Smartly with Diabetes: Using PWP and Mobile PWP for Self-Management	NLM	NIDDK and NLM	NIDDK and NLM
Longitudinal Aging Study in India	NIA	NLM	Howard University
LONI (Laboratory of Neural Imaging) Image Data Archive	NIBIB	NIA	Harvard T.H. Chan School of Public Health
Lupus Family Registry	NIAMS	NIBIB	University of Southern California
Malaria Research Resources	NLM	NIAMS	Oklahoma Medical Research Foundation
Mass Casualty Management System (DIORAMA-II)	NLM	NLM	NLM
MedlinePlus	NLM	NLM	University of Massachusetts Amherst
Meeting Clinicians' Information Needs with Highly Tailored Knowledge Summaries	NLM	NLM	NLM
Metabolomics Workbench	NIDDK	NLM	University of Utah
Methotrexate Response in Treatment of UC (MERIT-UC) Trial	NIDDK	OD/OSC (Common Fund)	University of California, San Diego

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Mexican Health and Aging Study	NIA	NIDDK	University of North Carolina at Chapel Hill
MH-GRID (Minority Health Genomics and Translational Research Bio-Repository Database)	NIMHD	NIA	Universities of Pennsylvania, Maryland, and Wisconsin in the U.S. and Instituto Nacional de Estadística, Geografía e Informática (INEGI) in Mexico
Micro-Manager Open Source Microscopy Software	NIBIB	NIMHD	Morehouse School of Medicine
Midlife in the United States	NIA	NIBIB	University of California, San Francisco
Molecular Imaging and Contrast Agent Database (MICAD)	NCI and NLM	NIA	University of Wisconsin
Molecular Modeling Database (MMDB)	NLM	NLM	NLM
Monitoring the Future (MTF)	NIDA	NLM	NLM
Morehouse Healthcare Personalized (P4) Health for Women	NIMHD	NIDA	University of Michigan
Mouse Tumor Database	NCI	NIMHD	Morehouse School of Medicine
MSigDB	NCI	NCI	Jackson Laboratory
MRI Study of Normal Brain Development	NICHD	NCI	Eli and Edythe L. Broad Institute of MIT and Harvard
Multidisciplinary Approach to the Study of Pelvic Pain (MAPP) Research Network	NIDDK	NICHD, NIDA, NIMH, and NINDS	NIH
Multiscale Framework for Molecular Heterogeneity Analysis	NLM	NIDDK	Multiple (University of Pennsylvania, DCC)
Mutant Mouse Resource and Research Centers Informatics, Coordination and Service Center	OD/ORIP	NLM	Emory University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Nanomaterial Registry	NIBIB	OD/ORIP	University of California, Davis
National Addiction & HIV Data Archive Program	NIDA	NCI	RTI International
National Alzheimer's Coordinating Center	NIA	NIDA	University of Michigan
National Archive of Computerized Data on Aging	NIA	NIA	University of Washington
National Cell Repository for Alzheimer's Disease (NCRAD)	NIA		Inter-university Consortium of Political and Social Research
National Clinical Trials Network Data Archive	NCI	NIA	University of Indiana
National Consortium on Alcohol & Neurodevelopment in Adolescence	NIAAA	NCI	Alliance for Clinical Trials in Oncology, Canadian Cancer Trials Group, Children's Oncology Group, ECOG-ACRIN Cancer Research Group, NRG Oncology, and Southwest Oncology Group
National Database for Autism Research (NDAR)	NIMH	NIAAA	SRI International
National Endoscopic Database of the Clinical Outcomes Research Initiative	NIDDK	NIMH	NIMH
National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	NIAAA	NIDDK	Oregon Health & Science University
National Health and Aging Trends Study	NIA	NIAAA	NIAAA
National Health and Nutrition Examination Survey	NCI	NIA	Johns Hopkins University
National Health Interview Survey — Cancer Control Supplement	NCI	Multiple	NCHS and CDC

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
National Health Interview Survey (CDC)	NCCAM	NCI and CDC	NCHS and CDC
National Long-Term Care Survey	NIA	NCCAM	
National Longitudinal Alcohol Epidemiologic Survey (NLAES)	NIAAA	NIA	Duke University
National NeuroAIDS Tissue Consortium	NIMH	NIAAA	NIAAA
National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE)	NEI	NIMH, NINDS	University of Texas Medical Branch; University of California, San Diego; Reed Neurological Research Center; Mount Sinai Medical Center; EMMES Corporation; and University of Nebraska
National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members	NHLBI	NEI	NEI
National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)	NHLBI	NINDS	University of Rochester
National Social Life, Health, and Aging Project	NIA	NHLBI and NIAMS	RTI International
NCATS Pharmaceutical Collection	NCATS	NIA	University of Chicago
NCBI BioSystems Database	NLM	NCATS	NCATS
NCBI Epigenomics	NLM	NLM	NLM
NCBI Taxonomy Database	NLM	NLM	NLM
NCI Genomics Data Commons	NCI	NLM	NLM
NDEx	NCI	NCI	NCI

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
NEIBANK: EST Analysis and Bioinformatics for Ocular Genomics	NEI	NCI	University of California, San Diego
Nephrotic Syndrome Study Network (NEPTUNE)	NIDDK	NEI	NEI
Neurobiology of Adolescent Drinking in Adulthood (NADIA)	NIAAA	NIDDK	Multiple (University of Michigan, DCC)
Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC)	NIBIB	NIAAA	University of North Carolina at Chapel Hill
Neuro-QOL: Quality of Life Outcomes Instrument for CNS Diseases	NINDS	NIBIB, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIMH, NINDS, and NINR	Turner Consulting Group, Inc.
NewDrugTargets.org	NCI	NINDS	Northwestern University Feinberg School of Medicine
NHLBI Biologic Specimen Repository	NHLBI	OD/OSC (Common Fund)	University of New Mexico
NIA Genetics of Alzheimer's Disease Data Storage Site	NIA	NHLBI	Precision Bioservices Inc.
NIA Primate Aging Database	NIA	NIA	University of Pennsylvania
NICEATM Local Lymph Node Database	NIEHS/NICEATM	NIA	University of Wisconsin–Madison
NIDA Center for Genetics Research	NIDA	NIEHS/NICEATM	NIEHS/NICEATM
NIDCD National Temporal Bone, Hearing, and Balance Pathology Resource Registry	NIDCD	NIDA	Rutgers, the State University of New Jersey, with subcontract to Washington University at St. Louis
NIDDK Central Repository: Biosample Repository	NIDDK	NIDCD	Massachusetts Eye and Ear
NIDDK Central Repository: Data Repository	NIDDK	NIDDK	Fisher BioServices

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
NIDDK Central Repository: Genetics Repository	NIDDK	NIDDK	Information Management Services, Inc.
NIDDK Inflammatory Bowel Disease Genetics Consortium Repository Database	NIDDK	NIDDK	Rutgers, the State University of New Jersey
NIDDK Information Network (dkNET)	NIDDK	NIDDK	Yale University
NIH AIDS Research and Reference Reagent Program	NIAID	NIDDK	University of California, San Diego
NIH Blueprint Neuroscience Information Framework	NIDA	NIAID	Fisher BioServices
NIH Common Data Elements (CDE) Repository	NLM	NIBIB, NCCAM, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS, and NINR	University of California, San Diego
NIH Human Embryonic Stem Cell (hESC) Registry	OD/OSP	NLM	NLM
NIH NeuroBioBank	NIMH	OD/OSP	OD/OSP
NIH Pediatric MRI Data Repository Clinical Coordinating Center	NICHD	NICHD, NIMH, and NINDS	NIH, University of Miami Brain Endowment Bank, University of Maryland Brain and Tissue Bank, Harvard Brain Tissue Resource Center, Sepulveda Research Corporation, Mount Sinai Brain Bank, and University of Pittsburgh Brain Tissue Donation Program
NIH Pediatric MRI Data Repository Data Coordinating Center	NIMH	NIDA, NIMH, and NICHD	Washington University
NIH Pediatric MRI Data Repository Data Coordinating Center	NINDS	NIDA, NIMH, and NICHD	McGill University and NIH

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
NIH Stem Cell Data Management System	NINDS	NIDA, NIMH, NICHD, and NINDS	Boston Children's Hospital, Children's Hospital Medical Center of Cincinnati, Children's Hospital of Philadelphia, University of California at Los Angeles, University of Texas Health Science Center, and Washington University
NIH Tetramer Core Facility	NIAID	NINDS	NIH Stem Cell Unit and NINDS Division of Intramural Research
NIHSeniorHealth	NLM	NIAID	Emory/Yerkes
NIMH Chemical Synthesis and Drug Supply Program	NIMH	NLM	NLM
NIMH Human Brain Collection Core	NIMH	NIMH	RTI International
NIMH Repository and Genomics Resource	NIMH	NIMH	NIMH
NINDS Common Data Elements	NINDS	NIMH	Washington University in St. Louis; Rutgers, the State University of New Jersey; and University of Southern California
NINDS Human Cell and Data Repository	NINDS	NINDS	KAI Research, Inc.
NLM Catalog	NLM	NINDS	Rutgers, the State University of New Jersey
Nonalcoholic Steatohepatitis Clinical Research Network's Nonalcoholic Fatty Liver Disease (NAFLD) Database (Adult and Pediatric)	NIDDK	NLM	NLM
Nonhuman Primate HIV/SIV Vaccine Trials Database	NIAID	NIDDK	Multiple (Johns Hopkins University, DCC)
Nonneoplastic Lesion Atlas	NTP	DOE and NIAID	Los Alamos National Laboratory

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
North American AIDS Cohorts Collaboration on Research and Design	NIAID	NIEHS/NTP	NTP
Novel Markers of Prognosis in Hypertrophic Cardiomyopathy (HCMR)	NHLBI	NIAID and NCI	Johns Hopkins University
Novel Therapies for Alcoholic Hepatitis - Informatics Core	NIAAA	NHLBI	University of Virginia
NTP Historical Control Database	NIEHS/NTP	NIAAA	Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Nuclear Receptor Signaling Atlas	NIDDK	NIEHS/NTP	NIEHS/NTP
Nucleotide	NLM	NIDDK, NICHD, and OD	Baylor College of Medicine
Observational Antiretroviral Studies in Southern Africa (OASIS) Collaboration	NIAID	NLM	NLM
OmniSearch	NCI	NIAID	University of Bern, Switzerland
Online Mendelian Inheritance In Animals (OMIA)	NLM	NCI	University of South Alabama
Online Mendelian Inheritance in Man (OMIM)	NHGRI	NLM	NLM
Open-i Image/Text Search System	NLM	NHGRI	Johns Hopkins University
OptiRNAi 2.0	NCI	NLM	NLM
Orthopedic Image Dataset	NLM	NCI	NCI
Osteoarthritis Initiative (OAI) Data Coordination Center	NIAMS	NLM	University of Southern California
Ovarian Kaleidoscope Database	NICHD	NIBIB, NIA, and ORWH	University of California, San Francisco

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
PACEmaker and Beta-Blocker Therapy Post-Myocardial Infarction	NHLBI	NICHD	Applied Bio Info
Panel Study of Income Dynamics	NIA	NHLBI	Northwestern University at Chicago
Papillomavirus Episteme (PaVE)	NIAID	NIA	University of Michigan
Pathosystems Resource Integration Center (PATRIC)	NIAID	NIAID	NIAID
Pathway Commons: A Public Library of Biological Pathways	NHGRI	NIAID	University of Chicago
Pathway Interaction Database Support	NCI	NHGRI	Sloan Kettering Institute
PaVE Papillomavirus Bioinformatics Resource	NIAID	NCI	NCI
Pediatric Acute Liver Failure Study Group	NIDDK	NIAID	NIH
Pediatric Cardiomyopathy Registry	NHLBI	NIDDK	Multiple (University of Pittsburgh, DCC)
Pediatric Imaging, Neurocognition, and Genetics (PING)	NIDA	NHLBI	University of Miami School of Medicine
Pediatric Myelodysplastic Syndrome and Bone Marrow Failure Patient Registry	NIDDK	NIDA	University of California, San Diego
Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB)	NIGMS	NIDDK	Children's Hospital Corporation, Boston
Physical Sciences-Oncology Network Bioresource Core Facility (PBCF)	NCI	NLM	Stanford University
Physical Sciences-Oncology Network Data Coordinating Center (PS-ON DCC)	NCI	NCI	ATCC

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Pillbox	NLM	NCI	NCI
Pleuropulmonary Blastoma DICER1 Syndrome Study	NCI	NLM	NLM
PopSet	NLM	NCI	International Pleuropulmonary Blastoma Registry; International Ovarian and Testicular Stromal Tumor Registry; Children's nationa and St. Louis Children's Hospital
PorA VR3 Typing Database	NIAID	NLM	NLM
Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT Study)	NIDDK	NIAID	NIAID
Prevention of Renal Damage in Primary Hyperoxaluria	NIDDK	NIDDK	Connecticut Children's Medical Center
PRISMS Informatics Platform – Federated Integration Architecture	NIBIB	NIDDK	Mayo Clinic, Rochester
PRISMS: Data and Software Coordination and Integration Center (DSCIC)	NIBIB	NIBIB	University of Utah
Probe	NLM	NIBIB	University of Southern California
Profiles in Science	NLM	NLM	NLM
Project MATCH Data Base	NIAAA	NLM	NLM
Prostate Cancer Prevention Trial (PCPT) Biorepository	NCI	NIAAA	University of Connecticut Health Center
Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO): Etiology and Early Marker Studies	NCI	NCI	Southwest Cooperative Oncology Group (SWOG)
Protein	NLM	NCI	NCI
Protein Capture Reagents Data Portal	NHGRI	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Protein Clusters	NLM	OD/OSC (Common Fund)	NCI
Protein Data Bank	NSF	NLM	NLM
PubChem	NLM	DOE, NIGMS, NLM, NSF, and NCI	Rutgers, the State University of New Jersey; and University of California, San Diego
Public HIV Drug Resistance Database	NIAID	NLM	NLM
Public Use Data on Mexican Immigration	NICHD	NIAID	Stanford University
PubMed Central	NLM	NICHD	Princeton University
PubMed Health	NLM	NLM	NLM
PubMed/Medline	NLM	NLM	NLM
qPrimerDepot	NCI	NLM	NLM
Radiation Emergency Medical Management (REMM)	NLM	NCI	NCI
Radiation Emergency Medical Management (REMM) Mobile	NLM	NLM	NLM
RAND Survey Meta Data Repository	NIA	NLM	NLM
Rat Genome Database	NHLBI	NIA	University of Southern California
Reference Sequence Database (RefSeq)	NLM	NHLBI, NCI, NEI, NHGRI, NIA, NIAAA, NICHD, NIDCD, NIDDK, NIMH, and NINDS	Medical College of Wisconsin
Registry and Surveillance for Hemoglobinopathies	NHLBI	NLM	NLM
Registry for Eosinophilic Gastrointestinal Disorders,	NIAID	NHLBI	CDC

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Consortium of Eosinophilic Gastrointestinal Disease Researchers, Rare Diseases Clinical Research Network			
Repbase Update, a Database of Repetitive Sequences	NLM	NIAID, NIDDK, and NCATS	Multiple (Cincinnati Children's Hospital Medical Center, DCC)
Repository of Molecular Brain Neoplasia Data (REMBRANDT)	NCI and NINDS	NLM	Genetic Information Research Institute
Research Resource for Complex Physiologic Signals	NIGMS	NCI	NCI
ResearchMatch	NCATS	NIGMS and NIBIB	Beth Israel Deaconess Medical Center
Restoring Insulin Secretion Study (RISE)	NIDDK	NCATS	Vanderbilt University
Retrovirus Epidemiology Study III (REDS III)	NHLBI	NIDDK	Multiple (George Washington University, DCC)
Retrovirus Resources	NLM	NHLBI	RTI International
RGAP: The Heritable Transcriptome and Alcoholism	NIAAA	NLM	NLM
RUMI: A Patient Portal for Retrieving Understandable Medical Information	NLM	NIAAA	University of Colorado Denver
RxIMAGE: Image Dataset of Prescription Pills	NLM	NLM	University of California, Los Angeles
RxNorm	NLM	NLM	NLM
Salivary Gland Molecular Anatomy Project	NIDCR	NLM	NLM
Salivary Gland Tumor Biorepository	NIDCR	NIDCR	NIDCR
Salivary Proteome Wiki Project	NIDCR and CIT	NIDCR	MD Anderson Cancer Center

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Sample Collection Registry for Quality Control of Biological and Environmental Specimens and Assay Development and Testing	NIEHS	NIDCR and CIT	NIH
Sea Urchin Genome Database (SpBase)	NICHD	NIEHS	NIEHS
SEARCH for Diabetes in Youth Study	NIDDK and CDC	NICHD	California Institute of Technology
SEER-Medicare Data	NCI	NIDDK and CDC	Multiple (Wake Forest School of Medicine, DCC)
SEER-Medicare Health Outcomes Survey Linked Database	NCI	NCI	NCI
Selenium and Vitamin E Cancer Prevention Trial (SELECT) Biorepository	NCI	NCI	NCI
Semantic LAMHDI: Linking Diseases to Model Organism Resources	OD/ORIP	NCI	Southwest Cooperative Oncology Group (SWOG)
SenseLab: Integration of Multidisciplinary Sensory Data	NIDCD	OD/ORIP	Oregon Health and Science University
Sequence Read Archive (SRA)	NLM	NIDCD and NINDS	Yale University
Severe Chronic Neutropenia International Registry	NIAID	NLM	NLM
SHARE Israel	NIA	NIAID	University of Washington
Shared Database for the Study of Phonological Development	NICHD	NIA	
Shwachman-Diamond Syndrome International Registry and Repository	NIAID	NICHD	Carnegie-Mellon University
Sign Language Acquisition, Annotation, Archiving and Sharing Platform	NIDCD	NIAID and NICHD	Fred Hutchinson Cancer Research Center

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Single Cell Analysis Program Transcriptome (SCAP-T) Project	NIMH	NIDCD	Haskins Laboratories, Inc.
Single Nucleotide Polymorphism (dbSNP)	NLM	OD/OSC (Common Fund)	University of Pennsylvania
Small Area Estimates for Cancer Risk Factors & Screening Behaviors	NCI	NLM	NLM
SOLAR-Eclipse Computational Tools for Imaging Genetics	NIBIB	NCI	NCI
Spin Trap Database	NIEHS	NIBIB	University of Maryland
State Cancer Profiles	NCI	NIEHS	NIEHS
Stories of Our Men: American Indian/Alaska Native Colorectal Health	NLM	NCI and CDC	NCI
Structurization and Direct Search of Medical Image Data	NIBIB	NLM	Mayo Clinic, Rochester
Surveillance, Epidemiology, and End Results (SEER)	NCI	NIBIB	Johns Hopkins University
Survey of Health, Ageing, and Retirement in Europe	NIA	NCI	NCI
Swedish Adoption/Twin Study of Aging	NIA	NIA	Munich Center for the Economics of Aging
Systematic Data Curation and Integration to Link Models of Human Disease	OD/ORIP	NIA	Karolinska Institutet
Systems Genetics of Alcohol Response and Stress Effects in CNS	NIAAA	OD/ORIP	Princeton University
Technical, Relational, & Conditional Process Models of MI Efficacy: Meta-Analysis	NIAAA	NIAAA	University of Tennessee Health Science Center
Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS)	NIDDK	NIAAA	Brown University

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
The Biological Magnetic Resonance Data Bank (BMRB)	NIGMS	NIDDK	Multiple (Cincinnati Children's Hospital Medical Center, DCC)
The Cancer Imaging Archive	NCI	NIGMS	University of Wisconsin
The Chernobyl Tissue Bank	NCI	NCI	NCI
The EcoCyc Model Organism Database for *Escherichia coli*	NIGMS	NCI	Imperial College London
The Environmental Determinants of Diabetes in the Young (TEDDY)	NIDDK	NIGMS	SRI International
The International Epilepsy Electrophysiology Database	NINDS	NIDDK	Multiple (University of South Florida, DCC)
The LA PRISMS Center: The Biomedical REAl-Time Health Evaluation (BREATHE) Platform	NIBIB	NINDS	University of Pennsylvania
The Mass Spectrometry Interactive Virtual Environment (MassIVE)	NIGMS	NIBIB	University of California, Los Angeles
The MetaCyc & BioCyc Pathway/Genome Databases	NIGMS	NIGMS	University of California, San Diego
The NCI Funded Research Portfolio (NFRP)	NCI	NIGMS	SRI International
The United States Immunodeficiency Network (USIDNET)	NIAID	NCI	NCI
THS: Using Twitter and Big Data Analytics to Track and Predict Health Conditions	NLM	NIAID	Immune Deficiency Foundation
ToxFx	NIEHS/NTP	NLM	University of Puerto Rico at Mayagüez
Toxics Release Inventory (TRI)	NLM	NIEHS/NTP	NIEHS/NTP

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
TOXLINE (Toxicology Literature Online)	NLM	NLM	EPA
TOXMAP (Environmental Health Maps)	NLM	NLM	NLM
TOXNET (Toxicology Data Network)	NLM	NLM	EPA
Trace Assembly Archive	NLM	NLM	NLM
Transcriptional Atlas of Human Brain Development	NIMH	NLM	NLM
Transcriptome Resources	NIAID	NIMH, NINDS, and NIDA	Allen Institute for Brain Science, Yale University, and University of Southern California
Translational Research and Evolving Alcoholic Hepatitis Treatment (TREAT) consortium	NIAAA	NIAID	NIAID
Transplant Cancer Match Study	NCI	NIAAA	Virginia Commonwealth University
Transporter Classification Database (TCDB)	NIGMS	NCI	NCI and HRSA
Trauma-Related Database	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	NIGMS	Massachusetts General Hospital
Turning The Pages: Rare Historic Works	NLM	NIDDK	Multiple (George Washington University, DCC)
UMLS (Unified Medical Language System)	NLM	NLM	NLM
UniGene	NLM	NLM	NLM

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
UniProt Protein Sequence and Function Knowledgebase	NHGRI	NLM	NLM
United States Renal Data System (USRDS)	NIDDK	NHGRI and NIGMS	European Molecular Biology Laboratory
University of Maryland Brain and Tissue Bank	NICHD	NIDDK	NIDDK
University of Washington Center for Mendelian Genomics	NHGRI	NICHD	University of Maryland
URBAN ARCH Consortium	NIAAA	NHGRI and NHLBI	University of Washington
Using Medical Informatics Principles to Enhance Development and Dissemination of Clinical Practice Guidelines on Major Depressive Disorder	NLM	NIAAA	Boston Medical Center
Value Set Authority Center (VSAC)	NLM	NLM	American Psychiatric Foundation
VectorBase (Invertebrate Vectors of Human Pathogens)	NIAID	NLM	NLM
Vietnam Era Twin Study of Aging	NIA	NIAID	University of Notre Dame
Viral Genomes	NLM	NIA	Boston University
Virus Pathogen Resource (ViPR)	NIAID	NLM	NLM
Visible Human Project Full Body Finite-Element Phantom and Workflow	NLM	NIAID	Northrop Grumman Corporation and J. Craig Venter Institute
Vitamin D and Type 2 Diabetes Study	NIDDK	NLM	NEVA Electromagnetics, LLC
WHO's Study on Global Ageing and Adult Health	NIA	NIDDK, OD	Multiple (Tufts Medical Center, DCC)
Whole Genome Shotgun Sequences	NLM	NIA	World Health Organization

Project/Resource Title	Administering IC(s)	Funding IC(s)	Institutions
Wireless Information System for Emergency Responders (WISER)	NLM	NLM	NLM
Wisconsin Longitudinal Study	NIA	NLM	NLM
Wisconsin Registry for Alzheimer Prevention: Biomarkers of Preclinical AD	NIA	NIA	University of Wisconsin
World Report	FIC	NIA	University of Wisconsin, Madison
WormGUIDES (Global Understanding in Dynamic Embryonic Systems)	OD/ORIP	NIH	All NIH ICs; for others, see https://worldreport.nih.gov/about.cfm
Xenbase, the Xenopus Model Organism Database	NICHD	OD/ORIP	Yale University
XNAT Open Source Informatics for Imaging Research	NIBIB	NICHD,	Cincinnati Children's Hospital Medical Center
ZFIN: The Zebrafish Model Organism Database	NHGRI	NIBIB	Washington University
		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* (see Appendix A for details), NCI recently developed scientific frameworks for two recalcitrant cancers:

- *Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC)*[1451]
- *Scientific Framework for Small Cell Lung Cancer (SCLC)*[1452]

This appendix includes an assessment of the progress made in improving outcomes for individuals diagnosed with these cancers; 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 fourth leading cause of cancer-related death in both men and women, with a five-year relative survival rate of less than 5 percent. In part because pancreatic cancer is usually diagnosed at an advanced stage, the survival rate is extremely low compared with those of many other cancer types. During 2001–2010, the incidence of pancreatic cancer increased by more than 10 percent, while the mortality rate increased by almost 5 percent.

Small cell lung cancer has a similarly low five-year relative survival rate: 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 biennial reports indicates a request for relative survival rates, we prefer to use mortality rates. Relative survival rates may be misleading for at least two reasons. First, there may be lead-time bias, where diagnosis earlier in the disease but without an improved clinical response is recorded incorrectly as improvement. Second, relative survival rates focus only on those patients who develop the disease. This is an important consideration for SCLC, where tobacco consumption is an important risk factor, and probably to some degree for PDAC. For example, if decreased smoking led to a

[1451] http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf.
[1452] http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLC%20Congressional%20Response.pdf.

50 percent reduction in the incidence and mortality of SCLC, this should be seen as progress, even if there were no change in relative survival rate. Mortality rates do not have these shortcomings.

NCI calculates mortality rates by using population-level data collected through its Surveillance, Epidemiology, and End Results program. In looking to assess progress made in improving these 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 a number of years after diagnosis in order to calculate accurate rates. Data that will be used to calculate relative mortality rates for patients diagnosed with PDAC and SCLC in recent years are still being collected.

As described in detail in the *Scientific Framework for PDAC*[1451] and the *Scientific Framework for SCLC*,[1452] NCI is supporting critical research in each of these disease areas that aims to improve outcomes. Scientific progress is being made to better understand both PDAC and SCLC, and NCI is continuing to prioritize research in these areas in an effort to translate this progress to improved prevention, diagnosis, treatment, and quality of life for patients.

Update on PDAC Activities (2014–2015)

NCI convened a panel of experts for the workshop to develop the scientific framework for PDAC in October 2012. The workshop report, *Pancreatic Cancer: Scanning the Horizons for Focused Interventions*,[1453] 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*,[1454] submitted to Congress in February 2014, provides the background, rationale, and implementation plans for four initiatives proposed to expand PDAC research. These initiatives are summarized below:

- *Understand the Biological and Clinical Relationship Between PDAC and Recent Onset Diabetes Mellitus.* Clinical and genetic epidemiological studies have identified an association between recent diagnosis of DM and subsequent diagnosis of PDAC. An in-depth understanding of the biological and clinical relationship between the two must be developed.

1. June 2013: NIDDK and NCI held a joint workshop on pancreatitis, diabetes, and pancreatic cancer.

    - October 2014: NIDDK and NCI issued a joint RFA for a Consortium to Study Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CSCPDPC) and a Coordination and Data Management Center: RFA-DK-14-27, RFA-DK-14 28 (U01). In September 2015, 10 clinical centers and a data management center were selected and approved for funding.

[1453] https://deainfo.nci.nih.gov/advisory/ctac/archive/0313/PCwgReport.pdf.
[1454] https://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/pdacframework.pdf.

- July 2015: NIDDK and NIBIB sponsored a workshop: "Advances in Biomedical Imaging, Bioengineering, and Related Technologies for the Development of Biomarkers of Pancreatic Disease."

- *Develop New Molecular and Imaging Biomarkers for Early Detection of PDAC and Its Precursors.* The goal of early detection strategies is to identify patients with the earliest-stage pancreatic cancers, precursor lesions, which have the best chance of cure. This will require a multidisciplinary effort from pancreatic cancer imaging, surgery, pathology, and epidemiology communities.

  - June 2015: NCI issued a PAR (Program Announcement with special receipt, referral, and/or review) for the Pancreatic Cancer Detection Consortium (U01): NCI PAR-15-289. November 2015 is the first receipt date for the PAR.

- *Implement New Immunotherapy Approaches Based on a Deeper Understanding of How PDAC Interacts With Its Potentially Immunosuppressive Microenvironment.* Recent data indicate that promotion of T-cell–dependent antitumor immunity can produce tumor regressions in patients with metastatic pancreatic cancer.

  - The Cancer Immunotherapy Trials Network (CITN) has prioritized pancreatic cancer immunotherapy studies.

- *Develop New Treatment Strategies That Interfere With RAS Oncogene-Dependent Signaling Pathways.* Development of strategies that neutralize RAS are needed.

  - In September 2014, a joint webinar between NCI's RAS Initiative at the Frederick National Laboratory for Cancer Research and the PDAC Progress Working Group was held.

  - In November 2015, the "RAS Immunotherapy Workshop" was held.

An *Interim Progress Report*[1455] on the PDAC Progress Working Group was provided to CTACin November, 2015. Specific language was added to the Cancer Clinical Investigator Team Leader Award announcement to encourage applications from candidates with research focuses on PDAC and SCLC beginning in 2015.

Update on Small Cell Lung Cancer Activities (2014–2015)

NCI convened a panel of experts for a workshop to develop a scientific framework for SCLC in July 2013. The workshop report, *Small Cell Lung Cancer: Seizing on Opportunities to Translate Recent Research into the Clinic for New Diagnostics and Interventions*,[1456] was developed over the following year and was presented to and accepted by CTAC in June 2014.

[1455] http://deainfo.nci.nih.gov/advisory/ctac/1115/8-PDACwgReport.pdf.
[1456] http://deainfo.nci.nih.gov/advisory/ctac/0614/SCLCworkshopReport.pdf.

The *Scientific Framework for Small Cell Lung Cancer*,[1457] 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 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.

To engage the research community in continuing the research agenda described in the scientific framework and to identify new research opportunities, NCI proposed a joint workshop with the International Association for the Study of Lung Cancer (IASLC) in early 2015. The IASLC Small Cell Lung Cancer workshop was held in April 2015 and was attended by 200 investigators from the international research community. NCI scientific and program staff took part in the meeting and helped in its organization.

Specific language was added to the NCI Cancer Clinical Investigator Team Leader Award announcement to encourage applications with candidates with a research focuses on PDAC and SCLC beginning in 2015.

The NCI Thoracic Malignancy Steering Committee has made the “rapid testing of new agents and strategies for the treatment of (SCLC)” one of its strategic priorities for 2015.

[1457] http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLC%20Congressional%20Response.pdf.

FY 2014 and 2015 NCI Grants Related to Pancreatic Ductal Adenocarcinoma

Project Number	Title	Contact PI	Institution
DP2CA195761	Engineering Organelle Function To Rewire Cancer Cell Metabolism	Zoncu, Roberto	University of California, Berkeley
F30CA167910	K-Ras4A Trafficking And Signaling	Tsai, Frederick Deechen	New York University School of Medicine
F30CA167963	Defining PI3K P110alpha As A Therapeutic Target In Pancreatic Cancer	Carpenter, Eileen S.	State University of New York at Stony Brook
F30CA168063	Roles Of Mir-17-92 Cluster Micrornas In K-Ras-Induced Pancreatic Tumorigenesis	Quattrochi, Brian Joseph	University of Massachusetts Medical School, Worcester
F30CA177123	Transcriptional Coregulation In Pancreatic Adenocarcinoma Progression	Ferreira, Mark Jakob	University of Pennsylvania
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
F30CA186640	Integration Of Glycolysis With The Epithelial-Mesenchymal Transition	Spaulding, Robert T.	University of Louisville
F30CA192819	A Differentiation-Based Mechanism Limiting Pancreatic Tumor Initiation	Krah, Nathan Michael	University of Utah
F30CA196106	A Role For Macrophage Phenotype In Regulating Metastasis In Pancreatic Carcinoma	Lee, Jae	University of Pennsylvania

Project Number	Title	Contact PI	Institution
F30CA196124	Pro- And Anti-Phagocytic Signals On Pancreatic Cancer Regulate Tumor Macrophages	Liu, Mingen	University of Pennsylvania
F30CA200301	Mechanistic And Informatics Based Analysis Of STAT1 Actions In Pancreatic Cancer	Craven, Kelly Eileen	Indiana University–Purdue University Indianapolis
F31CA168350	SPARC As A Regulator Of Collagen Signaling In Pancreatic Cancer	Aguilera, Kristina Yolanda	UT Southwestern Medical Center
F31CA177153	Genome-Wide Case-Control Association Study Of Pancreatic Cancer In Jews	Streicher, Samantha Acson	Yale University
F31CA177163	Elucidating The Role And Regulation Of Epithelial Plasticity In Metastasis	Aiello, Nicole	University of Pennsylvania
F31CA180392	The Activity And Molecular Interactions Of Extracellular EMMPRIN	Kendrick, Agnieszka	University of Colorado Denver
F31CA180602	The Role Of Type III TGF-Beta Receptor In The Fibrotic Tumor Stroma	Hesler, Rachel	Duke University
F31CA180628	Defining The Role And Mechanism Of Pak1 In Supporting Pancreatic Cancer	Baker, Nicole Marie	University of North Carolina at Chapel Hill
F31CA180693	Targeting K-Ras Effector Signaling For Pancreatic Cancer Treatment	Hayes, Tikvah K.	University of North Carolina at Chapel Hill
F31CA180738	Genetic And Pharmacological Manipulation Of System Xc In Pancreatic Cancer	Badgley, Michael Alexander	Columbia University Irving Medical Center
F31CA183493	Tumor Expressed B7x Accelerates Disease And Is A	Ohaegbulam, Kim C.	Albert Einstein College of Medicine

Project Number	Title	Contact PI	Institution
	Novel Target For Immunotherapy		
F31CA186513	Intact Protein As A Cancer Fuel Source	Nofal, Michel	Princeton University
F31CA189757	The Role Of Cancer Associated Fibroblasts In Pancreatic Tumor Progression	Pitarresi, Jason R.	Ohio State 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.	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 of New York at Stony Brook
F31CA203563	Investigating The Role Of Novel Drug Target TBK1 In Pancreatic Cancer Pathogenesis	Brannon, Arthur Lee	University of Michigan
F32CA177072	Mechanisms Of Tumor Suppression By Epigenetic Regulators In Pancreatic Cancer	Livshits, Geulah Yevgeniya	Sloan Kettering Institute
F32CA180374	Deciphering The Role Of Eif5a/PEAK1 Pathway In Pancreatic Cancer	Fujimura, Ken	University of California, San Diego
F32CA180452	Developing An Anti-Sialyl-Lewisa Diabody For Immunopet Imaging Of Pancreas Cancer	Houghton, Jacob	Sloan-Kettering Institute
F32CA180606	Investigating Yaps Role During Pathogenesis Of Pancreatic Ductal Adenocarcinoma	Staley, Binnaz Kucuk	University of California, San Francisco

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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
F32CA192904	Finding Novel Pancreatic Cancer Oncogenes Using An Innovative 3D 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
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	University of North Carolina at Chapel Hill
K08CA137153	A Model For Preclinical Biomarker Discovery In Pancreatic Ductal Adenocarcinoma	Collisson, Eric	University of California, San Francisco
K08CA138907	CD40 Pathway In Pancreatic Adenocarcinoma	Beatty, Gregory L.	University of Pennsylvania

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K08CA142903	RNA Therapeutics For Pancreatic Cancer	White, Rebekah	Duke University
K08CA142904	Innovative Delivery Strategy For Casm Gene Therapy In Pancreatic Cancer	Camp, Ernest Ramsay	Medical University of South Carolina
K08CA172676	Exploration Of A Mutant P53 Reactivating Compound	Carpizo, Darren Richard	Rutgers Biomedical and Health Sciences
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 Offspri	De Assis, Sonia	Georgetown University
K22CA181611	Online Monitoring And Image-Guided Treatment Of Chemoresistant Micrometastases	Spring, Bryan Quilty	Northeastern University
K23CA148964	Dissecting The Mechanisms Of Immune Tolerance Within The Pancreatic Tumors Micro	Zheng, Lei	Johns Hopkins University
K23CA163672	Cyclophosphamide Modified GM-CSF Pancreatic Tumor Vaccine + Listeria-Mesothelin	Le, Dung T.	Johns Hopkins University
K25CA137222	Quantitative Glycoproteomics For Pancreatic Cancer Studies	Pan, Sheng	University of Washington
K25CA164248	Quantitative Optical Dosimetry Of Magnetic Nanoparticle Cancer Treatments	Kanick, Stephen Chad	Dartmouth College
K25CA166178	Targeted Therapy Of Neuroendocrine Cancers Via The Notch Signaling Pathway	Gong, Shaoqin	University of Wisconsin–Madison

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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 Karol	Stanford University
P01CA084203	Molecular Response and Imaging-based Combination Strategies for Optimal PDT	Hasan, Tayyaba	Massachusetts General Hospital
P01CA117969	Genetics and Biology of Pancreatic Ductal Adenocarcinoma	DePinho, Ronald Anthony	University of Texas MD Anderson Cancer Center
P01CA159992	Magnetic Resonance Imaging-Guided Cancer Interventions	Butts Pauly, Kim	Stanford University
P01CA163200	Targeting diet-induced promotion of Kras-initiated pancreatic adenocarcinoma	Eibl, Guido Erwin Michael	University of California, Los Angeles
P20CA192994	1/2: Partnership to study racial and ethnic differences in GI cancer biology	Li, Ellen	State University of New York at Stony Brook
P20CA192996	2/2 Partnership to Study Racial and Ethnic Differences in GI Cancer Biology	McCombie, William Richard	Cold Spring Harbor Laboratory
P50CA101955	UAB / UMN SPORE in Pancreatic Cancer	Buchsbaum, Donald J.	University of Alabama at Birmingham
P50CA102701	Mayo Clinic SPORE in Pancreatic Cancer	Petersen, Gloria M.	Mayo Clinic, Rochester
P50CA127297	SPORE in Pancreatic Cancer	Hollingsworth, Michael A.	University of Nebraska Medical Center

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P50CA130810	Translational Research in GI Cancer	Brenner, Dean E.	University of Michigan
R00CA155045	Mechanism-Based Therapies For Pancreatic Cancer Informed By Stromal Microrheology	Celli, Jonathan P.	University of Massachusetts Boston
R00CA158582	Role Of Epigenetic Regulators In Pancreatic Cancer	Tzatsos, Alexandros	George Washington University
R01CA033084	Mechanisms Of Murine Turmor Eradication By Immunotherapy	Greenberg, Philip D.	University of Washington
R01CA034610	TGFB-SMAD Signaling In Stem Cell Differentiation And Tumor Suppression	Massagué, Joan	Sloan-Kettering Institute
R01CA042978	Biological Activity Of Ras Oncogenes	Der, Channing J.	University of North Carolina at Chapel Hill
R01CA051210	Biochemical And Molecular Studies On NQO1. Design Of Less Toxic Hsp90 Inhibitors	Ross, David	University of Colorado Denver
R01CA054358	Epigenetic Drivers Of Cancer Progression	Feinberg, Andrew P.	Johns Hopkins University
R01CA055360	Mechanisms Of Signal Transduction By Ras Proteins	Bar-Sagi, Dafna	New York University School of Medicine
R01CA065910	Focal Adhesion Kinase - Tumor Biology And Therapeutics	Cance, William G.	Roswell Park Comprehensive Cancer Center
R01CA069122	Role Of Tgfbeta Alterations In Pancreatic Cancer	Freeman, James W.	University of Texas Health Science Center at San Antonio
R01CA075059	Dysregulation Of TGF Beta Action Pancreatic Cancer	Korc, Murray	Indiana University–Purdue University Indianapolis

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R01CA077575	Causes & Consequences Of Acid Ph In Tumors	Gillies, Robert J.	H. Lee Moffitt Cancer Center & Research Institute
R01CA082683	Signal Transduction By Tyrosine Phosphorylation	Hunter, Tony R.	Salk Institute for Biological Studies
R01CA094184	Rala Signal Transduction	Counter, Christopher M.	Duke University
R01CA096924	Detection And Diagnosis Of Pancreatic Carcinoma	Gold, David V.	Center for Molecular Medicine and Immunology
R01CA097022	Survival Mechanisms Of Invasive Carcinoma Cells	Klemke, Richard, L.	University of California, San Diego
R01CA097061	Chemical Genetic Profiling Of Engineered Tumor Cells	Stockwell, Brent R.	Columbia University in the City of New York, Morningside
R01CA104125	Cytoskeletal Dynamics In Pancreatic Cancer Metastasis	Mc Niven, Mark A.	Mayo Clinic, Rochester
R01CA109525	Mouse Model For Human Pancreatic Ductal Adenocarcinoma	Su, Gloria Huei-Ting	Columbia University Irving Medical Center
R01CA112537	Embryonic Signaling Pathways In Pancreatic Cancer	Hebrok, Matthias	University of California, San Francisco
R01CA113669	Developmental Signaling Pathways In Pancreatic Cancer	Maitra, Anirban	University of Texas MD Anderson Cancer Center
R01CA122589	Function And Mechanism Of REDD1/Mtor Signaling In Metabolism And Tumorigenesis	Ellisen, Leif W.	Massachusetts General Hospital
R01CA123031	Dynamic Requirements Of Ras Signaling During Cancer	Counter, Christopher M.	Duke University

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R01CA124586	Kras-Induced Cellular Plasticity In Pancreatic Cancer	Konieczny, Stephen F.	Purdue University
R01CA124723	The Inhibition Of HSP70 Induces Apoptosis In Pancreatic Cancer Cells	Saluja, Ashok K.	University of Minnesota
R01CA131045	ATDC Function In Human Pancreatic Adenocarcinoma	Simeone, Diane M.	University of Michigan
R01CA135274	Overcoming Pancreatic Tumor Resistance To Gemcitabine	Cui, Zhengrong	University of Texas at Austin
R01CA136526	Mechanism Of Pancreatic Carcinogenesis	Fernandez-Zapico, Martin Ernesto	Mayo Clinic, Rochester
R01CA138701	Role Of Dietary Zinc Transporter ZIP4 In Pancreatic Cancer	Li, Min	University of Oklahoma Health Sciences Center
R01CA138723	Mechanism-Based Use Of Chk1 Inhibitors In Pancreas Cancer	Maybaum, Jonathan	University of Michigan
R01CA140182	Protein Kinase D In Oncogenic Oxidative Stress Signaling	Storz, Peter	Mayo Clinic, Jacksonville
R01CA140290	Role Of PKC Iota In Metaplasia And Initiation Of Pancreatic Cancer	Murray, Nicole R.	Mayo Clinic, Jacksonville
R01CA140410	Function And Regulation Mechanisms Of Polo-Like Kinase 3 In Pancreatic Cancer	Chiao, Paul J.	University of Texas MD Anderson Cancer Center
R01CA140424	Targeting Ras-Ral GEF-Ral Effector Signaling For Pancreatic Cancer Treatment	Yeh, Jen Jen J.	University of North Carolina at Chapel Hill
R01CA140550	SIAH2-Dependent Proteolysis In Cell Migration, Tumor Growth And Cancer Metastasis	Tang, Amy H.	Eastern Virginia Medical School

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R01CA140582	Therapeutic Targeting Of Stratifin Structure And Function	Zhang, Jian-Ting	Indiana University–Purdue University Indianapolis
R01CA140875	Mouse Models To Dissect P53 Tumor Suppressor Function	Attardi, Laura D.	Stanford University
R01CA140940	Enhancing The Biomedical Computing Platform For Pancreatic Cancer Research	Sherman, Simon	University of Nebraska Medical Center
R01CA142669	Fluorophore-Conjugated Antibodies For Imaging And Resection Of GI Tumors	Bouvet, Michael	University of California, San Diego
R01CA142674	Mechanisms Of Overexpressed Trkb In Inducing Pancreatic Cancer Metastasis	Chiao, Paul J.	University of Texas MD Anderson Cancer Center
R01CA148954	Genetic Approaches To Pancreatic Cancer Progression	Xie, Keping	University of Texas MD Anderson Cancer Center
R01CA150142	Cellular Diversity And Clinical Relevance Of Stem Cells In Pancreatic Cancer	Matsui, William H.	Johns Hopkins University
R01CA150190	Targeting Pancreatic Cancer Using Peptide Chemistry: From Bench To Bedside	Mukhopadhyay, Debabrata	Mayo Clinic, Rochester
R01CA151374	Evaluation Of In Vivo Optical Imaging In Pancreatic And Ovarian Cancer Patients	Martin, Lainie P.	Fox Chase Cancer Center
R01CA151588	Gli Activity In The Pancreas: Inflammation, Tissue Repair And Cancer	Pasca di Magliano, Marina	University of Michigan
R01CA152309	Functional Validation Of Pancreatic Cancer Progression Biomarker	Xie, Keping	University of Texas MD Anderson Cancer Center

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R01CA153821	G-Quadruplex-Mediated Transcriptional Regulation Of PDGFR-??	Hurley, Laurence H.	University of Arizona
R01CA154172	Phospho-Valproic Acid For Pancreatic Cancer Prevention	Rigas, Basil	State University of New York at Stony Brook
R01CA154321	Prevention Of Tumor Progression By A Novel Approach	Sarkar, Fazlul H.	Wayne State University
R01CA154383	Multipotential Mesenchymal Stem Cell-Like Cells In Pancreatic Tumorigenesis	Bergers, Gabriele	University of California, San Francisco
R01CA154517	Disclosing Genomic Incidental Findings In A Cancer Biobank: An ELSI Experiment	Petersen, Gloria M.	Mayo Clinic, Rochester
R01CA154586	The Anti-Senescence Activity Of Trefoil Factor 1	Wang, Xiao-Fan	Duke University
R01CA154823	Validation And Fine-Scale Mapping Of Pancreatic Cancer Susceptibility Loci	Klein, Alison P.	Johns Hopkins University
R01CA154846	MRI Capable Receptor Targeted Drug Delivery For Pancreatic Cancer	Mao, Hui	Emory University
R01CA155198	Design Of MEK Inhibitor Regimens For The Treatment Of Pancreatic Cancer	Leopold, Judith S.	University of Michigan
R01CA155620	RON Receptor In Pancreatic Cancer Biology And Therapy	Lowy, Andrew M.	University of California San Diego
R01CA155784	Dissecting Hedgehog, TGF Beta And BMP Signaling During Pancreatic Tumorigenesis	Lewis, Brian C.	University of Massachusetts Medical School, Worcester

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R01CA157490	Investigating The Role Of Autophagy In Pancreatic Cancer Radiation Resistance	Kimmelman, Alec	Dana-Farber Cancer Institute
R01CA157738	Novel Single Domain Antibodies With Multivalency And Multispecificity	Liu, Rihe	University of North Carolina at Chapel Hill
R01CA157980	Mechanisms Of The Stromal Response To Smoothened Inhibition In Pancreatic Cancer	Olive, Kenneth P.	Columbia University Irving Medical Center
R01CA159222	ADAM17 In Pancreatic Cancer And Pancreatitis	Crawford, Howard C.	University of Michigan
R01CA160417	Targeting HMGB1-Mediated Autophagy In Cancer Therapy	Tang, Daolin	University of Pittsburgh
R01CA160924	The Role Of Telomere-Related Tetraploidization In Cancer	de Lange, Titia	Rockefeller University
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
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	Ikkalpha, 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
R01CA163907	Interactions Of The Angiopoietin And PD-ECGF Pathways In Tumor Angiogenesis	Schwartz, Edward L.	Albert Einstein College of Medicine
R01CA164041	Aldo-Keto Reductase Family 1 Member B10 AKR1B10 In Pancreatic Carcinogenesis	Yang, Guang-Yu	Northwestern University at Chicago
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 Irving Medical Center
R01CA167291	Novel Role Of Ref-1 In Pancreatic Cancer Etiology And Progression	Kelley, Mark R.	Indiana University–Purdue University Indianapolis
R01CA167535	Novel Nanoparticle Therapy For Pancreatic Cancer	Matters, Gail L.	Penn State Health Milton S. Hershey Medical Center

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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.	University of Virginia
R01CA168863	Ccr2 Blockade In Human Pancreatic Cancer	Linehan, David C.	University of Rochester
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	University of Texas Health Science Center at Houston
R01CA169123	Immunobiology And Immunotherapy Of Pancreatic Cancer	Vonderheide, Robert H.	University of Pennsylvania
R01CA169281	Targeting Stromal Collagen In Pancreatic Cancer	Han, Haiyong	Translational Genomics Research Institute
R01CA169702	Annexin A2 As A Mediator Of Pancreatic Cancer Metastases	Zheng, Lei	Johns Hopkins University

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R01CA170495	A Drosophila Model Linking Diet-Induced Obesity And Cancer (PQ 1)	Cagan, Ross Leigh	Icahn School of Medicine at Mount Sinai
R01CA170911	Deciphering The Tissue Specificity Of MEN1 Related Tumorigenesis	Libutti, Steven Kenneth	Albert Einstein College of Medicine
R01CA170946	Triptolide Augments Death Receptor Mediated Apoptosis In Pancreatic Cancer	Saluja, Ashok K.	University of Minnesota
R01CA172045	Epigenetic Regulation Of Pancreatic Cancer	Hebrok, Matthias	University of California, San Francisco
R01CA172233	Molecular Mediators Of Pancreatic Cancer Invasion And Progression	Xie, Keping	University of Texas MD Anderson Cancer Center
R01CA172380	Determining The Roles Of ATRX And DAXX Abnormalities In Cancer Telomere Biology	Meeker, Alan Keith	Johns Hopkins University
R01CA172431	Inhibition Of Pancreatic Carcinogenesis Via Targeting C-Raf And Seh	Yang, Guang-Yu	Northwestern University at Chicago
R01CA172560	Mechanisms Of Action Of The Smyd3 Methyltransferase In Cancer Cells	Gozani, Or P.	Stanford University
R01CA172880	Advanced Glycation End-Products And Risk Of Pancreatic Cancer	Jiao, Li	Baylor College of Medicine
R01CA174294	Multifunctional Immunopet Tracers For Pancreatic And Prostate Cancer	Wu, Anna M.	University of California, Los Angeles
R01CA174388	Single-Cell Phenotyping For Therapeutic Stratification In Pancreatic Cancer	Wirtz, Denis	Johns Hopkins University

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R01CA174861	Novel Theranostics For Pancreatic Cancer	Davydova, Julia	University of Minnesota
R01CA175747	Mechanisms Of PAK1 Activation, Signaling And Tumor Resistance	Der, Channing J.	University of North Carolina at Chapel Hill
R01CA175772	Targeting Tumor-Stromal Interaction For Pancreatic Cancer Therapy	Singh, Ajay Pratap	University of South Alabama
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
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 Irving Medical Center
R01CA178627	Novel Experimental Therapeutics For Pancreatic Cancer	Lomberk, Gwen	Mayo Clinic, Rochester
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

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R01CA180057	(PQD6) Muscle Stem Cells And Cancer Cachexia	Guttridge, Denis C.	Ohio State University
R01CA180949	Early Detection Of Pancreatic Cancer In Diabetics	Chen, Ru	University of Washington
R01CA181185	Inhibition Of CDC25B Phosphatase By Targeting Protein-Protein Interactions	Cierpicki, Tomasz	University of Michigan
R01CA181244	Discovery Of Risk Loci And Genomics Of Pancreatic Cancer Through Exome Sequencing	Scheet, Paul A.	University of Texas MD Anderson Cancer Center
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.	University of Pittsburgh
R01CA182076	Biomarker Validation For Intraductal Papillary Mucinous Neoplasms Of The Pancreas	Allen, Peter J.	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	University of Oklahoma Health Sciences Center
R01CA183101	Biophotonics To Couple Pancreatic With Upper GI Screening Via Ultrathin Endoscopy	Backman, Vadim	Northwestern University

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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.	University of Iowa
R01CA184274	Functional Significance Of CD133 In Pancreatic Cancer	Banerjee, Sulagna	University of Minnesota
R01CA184687	Pancreatic Cancer Vulnerabilities Downstream Of Cooperating Oncogenic Mutations	Land, Hartmut	University of Rochester
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	Johns Hopkins University
R01CA186043	Musashi-Mediated Control Of Pancreatic Cancer Growth And Progression	Reya, Tannishtha	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	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 at Chicago

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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	University of California, Los Angeles
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
R01CA188252	ROS-Targeted Therapy For Pancreatic Cancer	Neamati, Nouri	University of Michigan
R01CA188300	Motion Management Of Pancreatic Cancer In MRI-Guided Radiotherapy	Sheng, Ke	University of California, Los Angeles
R01CA188464	Epigenetic Priming In Pancreatic Cancer Chemotherapy	Govindarajan, Rajgopal	Ohio State University
R01CA188654	MR-HIFU Induced Drug Delivery For Pancreatic Cancer Treatment	Lee, Donghoon	University of Washington
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

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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.	University of Texas Southwestern Medical Center
R01CA193650	The Adaptive Kinome In Pancreatic Cancer	Yeh, Jen Jen J.	University of North Carolina at Chapel Hill
R01CA194593	PQB3: Mechanisms & Targeting Of Sonic Hedgehog Signaling In Muscle Wasting Of Cancer Cachexia	Zimmers, Teresa A.	Indiana University–Purdue University Indianapolis
R01CA195473	Repurposing Disulfiram: A Novel Strategy To Help Cancer Patients Regain Muscle	Jatoi, Aminah	Mayo Clinic, Rochester
R01CA195586	Targeted Radiation Therapy For Pancreatic Cancer	Batra, Surinder K.	University of Nebraska Medical Center
R01CA195651	Clinical Significance Of Pancreatic Cancer Differentiation And Dedifferentiation	Xie, Keping	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	University of Texas MD Anderson Cancer Center
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

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R01CA197296	Reprogramming The Pancreatic Tumor Microenvironment With Immunotherapy	Zheng, Lei	Johns Hopkins University
R01CA198074	Dosage-Dependent Hedgehog Signaling In Pancreatic Cancer	Allen, Benjamin	University of Michigan
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.	State University of New York at Buffalo
R03CA166664	Role Of Obesity-Induced Immunosuppression In Pancreatic Cancer	Rogers, Connie J.	Pennsylvania State University, University Park
R03CA166910	MUC1 Regulation Of TGF-Beta Function In Pancreatic Cancer Cells	Mukherjee, Pinku	University of North Carolina at Charlotte
R03CA166912	Chemical Genetic Dissection Of Aurora A In Promoting EMT And Stem Cells Phenotype	Shah, Kavita	Purdue University
R03CA169692	Identification Of The Molecules/Pathways That Confer Acquired Radioresistance In	Du, Yuchun	University of Arkansas at Fayetteville
R03CA173223	Flt3L Treatment Of Pancreatic Cancer	Solheim, Joyce C.	University of Nebraska Medical Center
R03CA173273	Improving Pancreas RT Plans Using Respiration-Driven Anatomic Deformation	Yang, Wensha	Cedars-Sinai Medical Center

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R03CA179681	Pancreatic Cystic Lesions: Descriptive Epidemiology And Natural History	Bracci, Paige M.	University of California, San Francisco
R03CA181584	Targeting Cancer Stem Cell Initiation During Pancreatic Cancer Development	Mohammed, Altaf	University of Oklahoma Health Sciences Center
R03CA181727	A Novel Combination Approach For Pancreatic Cancer Prevention	Mackenzie, Gerardo Guillermo	State University of New York at Stony Brook
R03CA182552	A Novel Regimen To Target Both Pancreatic Cancer K-Ras And Antiapoptotic Proteins	Li, Fengzhi	Roswell Park Comprehensive Cancer Center
R03CA182679	Developing Nanotechnology To Target HMGA1 In Pancreatic Cancer	Smith-Resar, Linda M.	Johns Hopkins University
R03CA184544	Role Of Piceatannol In Cancer Cachexia	Kim, Kee-Hong	Purdue University
R03CA191621	Developing A Screen For Novel Therapies With Reprogrammed Pancreatic Cancer Cells	Smith-Resar, Linda M.	Johns Hopkins University
R03CA195453	Endoenteric Balloon Coils For Improved MR Imaging Of The Pancreas And Upper GI Tract	Hadley, John Rock	University of Utah
R15CA182834	Combinatorial Nanotechnology-Based Regimens For Pancreatic Cancer Chemoprevention	Prabhu, Sunil	Western University of Health Sciences
R15CA192160	Multifunctional Nanoparticles For Combinational Therapy Of Pancreatic Cancer	Vivero-Escoto, Juan Luis	University of North Carolina at Charlotte
R21CA164245	Non-Oncogene Addiction As A Targeted Therapy For Pancreatic Cancer	Faller, Douglas V.	Boston University Medical Campus

Project Number	Title	Contact PI	Institution
R21CA164756	Grp94 Targeted Therapy For Pancreatic Ductal Adenocarcinoma	Ferrone, Soldano	Massachusetts General Hospital
R21CA167329	NMDA Receptors In The Diagnosis And Treatment Of Pancreatic Cancer	North, William G.	Dartmouth College
R21CA169611	Targeting Telomerase In Pancreateic Cancer	Taylor, Derek James	Case Western Reserve University
R21CA169706	Chemosensitization Of Pancreatic Cancer Cells By Curcumin And Vitamin D Receptor	Yen, Timothy	Fox Chase Cancer Center
R21CA169717	Epi)Genomic Drivers Of Primary And Metastatic Pancreatic Islet Cell Carcinoma	Gross, Kenneth W.	Roswell Park Comprehensive Cancer Center
R21CA169720	Novel Anti-HER3 Strategy For Pancreatic Cancer	Zhou, Tong	University of Alabama at Birmingham
R21CA169741	The Role Of The Stromal Cell Surface Protease FAP In Pancreatic Cancer	Puré, Ellen	University of Pennsylvania
R21CA169757	Profiling Pancreatic Cancer Metabolism And Tumor Microenvironment For Therapy	Le, Anne	Johns Hopkins University
R21CA169844	Minimally Invasive Ablative Therapies For Pancreatic Cystic Neoplasms	Cuevas, Carlos	University of Washington
R21CA169849	Novel Cell Cycle Therapeutic Targets In Pancreatic Cancer	Dowdy, Steven F.	University of California, San Diego
R21CA170041	HDAC3 - A Therapeutic Target In PDA	Hayman, Michael John	State University of New York at Stony Brook

Project Number	Title	Contact PI	Institution
R21CA170121	Targeting Pancreatic Cancer With Aptamers To The CCK-B Receptor	Matters, Gail L.	Pennsylvania State University Hershey Med Center
R21CA170995	Anti-Pancreatic Tumorigenesis By Inactivation Of SAG/RBX2 E3 Ubiquitin Ligase	Sun, Yi	University of Michigan
R21CA172983	Anti-PV1 Therapy For Pancreatic Cancer	Stan, Radu Virgil	Dartmouth College
R21CA172997	Targeting RAS Signaling With CDK And AKT Inhibition In Pancreatic Cancer	Azad, Nilofer	Johns Hopkins University
R21CA173120	Therapy Of Pancreatic Cancer With 212Pb-Labeled B7-H3 Specific Ab And LDE225	Buchsbaum, Donald J.	University of Alabama at Birmingham
R21CA173297	Mechanisms Of Pancreatic Cancer Inhibition By SPARC	Cohn, Susan L.	University of Chicago
R21CA173348	Autophagy In Pancreatic Neuroendocrine Tumor Growth And Metastasis	Du, Yi-Chieh Nancy	Weill Medical College of Cornell University
R21CA173473	Optimizing Selective In Vivo Inhibition Of Pancreatic Tumor JAK2/STAT3 Signaling	Phelps, Mitch A.	Ohio State University
R21CA173487	Axl As A Target For The Therapy Of Pancreatic Cancer	Brekken, Rolf A.	University of Texas Southwestern Medical Center
R21CA173518	Breakdown Of Desmoplasia In Pancreatic Cancer To Enhance Drug Effectiveness	Boucher, Yves	Massachusetts General Hospital
R21CA173605	MUC1-Targeted Nanotherapy For Pancreatic Cancer	Winter, Jordan M.	Thomas Jefferson University

Project Number	Title	Contact PI	Institution
R21CA174306	IDO-Silencing Salmonella Therapy For The Treatment Of Primary And Metastatic PDAC	Diamond, Don J.	Beckman Research Institute of City of Hope
R21CA174594	Single Molecule Microarrays For The Detection Of Mutant DNA In Body Fluids	Celedon, Alfredo Andres	Scanogen Inc.
R21CA175699	Pancreatic Cancer Control By A Novel Combination Treatment	Mackenzie, Gerardo Guillermo	State University of New York at Stony Brook
R21CA175833	Use Of DND1 To Counteract Mirna Function In Cancers	Matin, Angabin	University of Texas MD Anderson Cancer Center
R21CA175974	Differential Network Interrogations Of Epithelial To Mesenchymal Transition	Mohammad, Ramzi M.	Wayne State University
R21CA176097	N-Cadherin And Metastatic Dissemination	Radice, Glenn Lawrence	Thomas Jefferson University
R21CA176222	Targeting RAGE In Pancreatic Cancer	Guzman, Esther Amalia	Florida Atlantic University
R21CA176267	C-Src Kinase-Calmodulin Interaction: A Therapeutic Target For Pancreatic Cancer	Krishna, Nepalli Rama	University of Alabama at Birmingham
R21CA176337	Development Of New Therapeutics For Pancreatic Cancer Management	Pietras, Richard Joseph	University of California, Los Angeles
R21CA176339	Stromal Depletion For Pancreatic Cancer Therapy	Li, Shyh-Dar	University of British Columbia
R21CA176364	Directional Motility And ERM Scaffolding In Pathfinder Pancreatic Carcinoma Cells	Mulder, Kathleen M.	Penn State Health Milton S. Hershey Medical Center

Project Number	Title	Contact PI	Institution
R21CA176535	Evaluation Of MSP Antagonists For The Treatment Of Pancreatic Cancer	Harding, Joseph W.	Washington State University
R21CA176561	A Genetically Defined System To Identify Factors Essential For Kras Oncogenesis	Collisson, Eric	University of California, San Francisco
R21CA178651	A RAS-FAM83A Regulatory Loop As A Novel Therapeutic Target For Pancreatic Cancer	Jackson, Mark W.	Case Western Reserve University
R21CA179193	ERK Inhibitor Resistance And ERK Isoform-Dependent Growth In Pancreatic Cancer	Der, Channing J.	University of North Carolina at Chapel Hill
R21CA179273	Targeting Cell Surface GRP78 As A Novel Therapy For Pancreatic Cancer	Lee, Amy S.	University of Southern California
R21CA179362	A Creative Integration Of Omega-3 Fatty Acids Into Pancreatic Cancer Chemotherapy	Cui, Zhengrong	University of Texas at Austin
R21CA179379	Role Of Trxralpha In Pancreatic Cancer Development And Therapy	Zhang, Xiao-Kun	Sanford Burnham Prebys Medical Discovery Institute
R21CA179453	An Epigenetic Switch Controlling Pancreatic Cancer Susceptibility	Murtaugh, Lewis C.	University of Utah
R21CA179489	Targeting Adipocyte Lipases To Treat Pancreatic Cancer-Associated Cachexia	Saez, Enrique	Scripps Research Institute
R21CA179541	Evaluation Of Positron Emission Tomography-Magnetic Resonance Imaging (Pet-Mri)	Fields, Ryan C.	Washington University
R21CA179668	The Role Of SHIP-1 In The Modulation Of	Ghansah, Tomar	University of South Florida

Project Number	Title	Contact PI	Institution
	Immunoregulatory Cells In Pancreatic Canc		
R21CA180764	An Inhibitor Of Multiple Anti-Apoptotic Gene Products For Pancreatic Cancer	Li, Fengzhi	Roswell Park Comprehensive Cancer Center
R21CA181851	Improving Radiation Therapy For Pancreatic Cancer	Wang, Xinhui	Massachusetts General Hospital
R21CA182608	Quantitative Spectroscopic Imaging Of Cancer Metabolites In Live Cells And Intact	Cheng, Ji-Xin	Purdue University
R21CA182651	Characterization Of Drug Survival By Pancreatic Cancer Cells In Vitro And In Vivo	Yen, Timothy	Fox Chase Cancer Center
R21CA182662	Elucidating And Targeting Epigenetic Oncogenic Networks In Pancreatic Cancer	Tzatsos, Alexandros	George Washington University
R21CA182692	Utilizing Hur To Optimize The Treatment Of Pancreatic Cancer	Brody, Jonathan	Thomas Jefferson University
R21CA182701	Targeting Ccr2 To Overcome Immunosuppression And Improve Immunotherapy	Denardo, David G.	Washington University
R21CA182820	Phosphorylated Form Of Activated Ikkbeta And Pancreatic Cancer	Natarajan, Amarnath	University of Nebraska Medical Center
R21CA182977	Multi-Tracer PET/CT Imaging Of Gemcitabine Response In Pancreatic Cancer	Kadrmas, Dan J.	University of Utah
R21CA184429	Perioperative Stromal Depletion Strategies In Pancreatic Ductal Adenocarcinoma	Tempero, Margaret A.	University of California, San Francisco

Project Number	Title	Contact PI	Institution
R21CA185209	Two Phospho-Compounds For Pancreatic Cancer Prevention	Mackenzie, Gerardo Guillermo	State University of New York at Stony Brook
R21CA185276	A New Energy Restriction Mimetic That Targets Pancreatic Cancer	Lanza-Jacoby, Susan Patricia	Thomas Jefferson University
R21CA185536	(PQC5)Early Detection Pancreatic Cancer By Hyperpolarized Silicon Nanoparticles	Bhattacharya, Pratip K.	University of Texas MD Anderson Cancer Center
R21CA185689	Non-Invasive Differentiation Of Benign Lesions From Aggressive Pancreatic Cancer	Craik, Charles Scott	University of California, San Francisco
R21CA185909	H3K9 Methylation And Pancreatic Cancer Chemoresistance	Liu, Kebin	Georgia Regents University
R21CA186175	Targeting DCLK1 Kinase Activity In Pancreatic Cancer	Houchen, Courtney Wayne	University of Oklahoma Health Sciences Center
R21CA186791	Needle Biopsy Preservation And Preparation For Rapid 3D Pathology Of Pancreas	Seibel, Eric. J	University of Washington
R21CA186957	Hedgehog Acyltransferase As A Target In Cancer	Resh, Marilyn D.	Sloan-Kettering Institute
R21CA187869	Detection Of 5-Hmc As A Novel Screening Biomarker For Pancreatic Cancer	Zhang, Wei	Northwestern University at Chicago
R21CA188059	Long Non-Coding Rnas In Pancreatic Cancer	Sussel, Lori	Columbia University Irving Medical Center
R21CA188818	Targeting PAK4 For Overcoming Drug Resistance In Pancreatic Cancer	Azmi, Asfar Sohail	Wayne State University

Project Number	Title	Contact PI	Institution
R21CA188857	Preclinical Evaluation Of A Targeted Bmi1 Inhibitor In Pancreatic Cancer	Olive, Kenneth P.	Columbia University Irving Medical Center
R21CA188858	Investigation Of Therapeutic Modulators Of Apoptotic Priming In Pancreatic Cancer	Letai, Anthony G.	Dana-Farber Cancer Institute
R21CA188863	Multiplexed In Vivo Drug Screening: Inhibitors Of Metastatic Seeding	Winslow, Monte Meier	Stanford University
R21CA188911	Adaptable Hydrogel Platform To Study Pancreatic Cancer	Lin, Chien-Chi	Indiana University–Purdue University Indianapolis
R21CA189477	Gpcrs: Novel Targets In Cancer-Associated Fibroblasts	Insel, Paul A.	University of California, San Diego
R21CA189775	Therapeutic Monitoring In Pancreatic Cancer Using An Exosome Based Mass Spec Assay	Lubman, David M.	University of Michigan
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.	Wayne State University
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.	Rutgers, The State University of New Jersey

Project Number	Title	Contact PI	Institution
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	Fox Chase Cancer Center
R21CA192629	Glycan Control Of Stem Cell-Associated Pathways In Pancreatic Cancer	Bellis, Susan L.	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	University of Utah
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
R21CA196485	High Specificity Microrna Microarray Analysis Without PCR For Cancer Screening And Research	Saraf, Ravi F.	University of Nebraska–Lincoln

Project Number	Title	Contact PI	Institution
R21CA198109	Deciphering SIRT6-Dependent Metabolic Liabilities In Pancreatic Cancer	Mostoslavsky, Raul	Massachusetts General Hospital
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	University of Texas MD Anderson Cancer Center
R33CA183685	Advanced Methods To Evaluate Extracellular Matrix And Crosslinking In The Tumor M	Hansen, Kirk C.	University of Colorado Denver
R35CA197562	Mediators Of Cancer Cell Homeostasis: Intervention Targets Common To Diverse Types Of Cancer	Land, Hartmut	University of Rochester
R35CA197591	Integrative Approaches To Elucidate P53 Transcriptional Networks During Carcinogenesis	Attardi, Laura D.	Stanford University
R41CA176931	Novel Small Molecule Therapeutics For Pancreatic Cancer	Okolotowicz, Karl J.	ChemRegen, Inc.
R41CA177288	Mucins In The Diagnosis And Prognosis Of Pancreatic Diseases	Sasson, Aaron R.	Sanguine Diagnostics And Therapeutics, Inc.

Project Number	Title	Contact PI	Institution
R43CA183265	Frostbite - A Unique Catheter For Endoscopic Cryoablation	Baust, John M.	CPSI Biotech
R43CA183280	Pancreatic-Cancer Imageable Patient-Derived Orthotopic Xenografts (Ipdox)	Yang, Meng	AntiCancer, Inc.
R43CA186424	Sting-Activating Gm-Csf Secreting Allogeneic Pancreas Tumor Cell Vaccine Therapy	Dubensky, Thomas W.	Aduro Biotech, Inc.
R43CA187852	B Cell Repertoire Molecular Platform For Antibody Drug Discovery	Johnson, David Scott	GigaGen, Inc.
R43CA189374	Therapeutic Antibody Discovery From Pancreatic Cancer B Cell Repertoires	Johnson, David Scott	GigaGen, Inc.
R43CA189436	Development Of An ADC Against Pancreatic Cancer	Schlosser, Michael J.	COARE Biotechnology, Inc.
R43CA195684	Development Of Novel Targeted Agents In Pancreatic Cancer	Sigalov, Alexander B.	SignaBlok, Inc.
R43CA199058	Profiling Circulating Mirna Without PCR For Early Detection Of Pancreatic Cancer	Saraf, Ravi F.	Vajra Instruments, Inc.
R44CA168158	Development Of Sephb4-HSA As Novel Therapeutic In Cancer	Krasnoperov, Valery G.	VasGene Therapeutics, Inc.
R44CA200186	Molecular MR Imaging Of The Desmoplastic Response In Pancreatic Cancer	Humblet, Valerie	Collagen Medical LLC
U01CA111294	Early Diagnosis Of Pancreatic Cancer	Hollingsworth, Michael A.	University of Nebraska Medical Center
U01CA111302	Biomarkers For The Early Detection Of Pancreatic Cancer	Killary, Ann M.	University of Texas MD Anderson Cancer Center

Project Number	Title	Contact PI	Institution
U01CA128454	Discovery And Development Of Cancer Glycomarkers	Pierce, J. Michael	University of Georgia
U01CA151455	Nanoscale Metal-Organic Frameworks For Imaging And Therapy Of Pancreatic Cancer	Lin, Wenbin	University of Chicago
U01CA151650	Magnetoresistive Sensor Platform For Parallel Cancer Marker Detection	Porter, Marc D.	University of Utah
U01CA151810	Theranostic Nano Particles For Targeted Treatment Of Pancreatic Cancer	Yang, Lily	Emory University
U01CA151886	Preclinical Platform For Theranostic Nanoparticles In Pancreatic Cancer	Halas, Nancy J.	Rice University
U01CA151925	Role Of Fibroblasts, Myeloid Cells And Matrix In PDAC	Kalluri, Raghu	University of Texas MD Anderson Cancer Center
U01CA152653	Detection Of Pre-Invasive Pancreatic Cysts Using Protein And Glycan Biomarkers	Haab, Brian B.	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
U01CA178960	Targeting Pancreatic Cancer Energy Metabolism, Tumor Growth, And Metastasis	Dwinell, Michael B.	Medical College of Wisconsin
U01CA187508	A Prospective Investigation Of The Oral Microbiome And Pancreatic Cancer	Palmer, Julie R.	Boston University Medical Campus

Project Number	Title	Contact PI	Institution
U01CA196403	Imaging And Molecular Correlates Of Progression In Cystic Neoplasms Of The Pancreas	Maitra, Anirban	University of Texas MD Anderson Cancer Center
U01CA198846	UCLA Multifunctional Mesoporous Silica Nanoparticle Platform For Treatment Of Pancreas Cancer	Nel, Andre Elias	University of California, Los Angeles
U01CA198913	Stroma Breaking Theranostic Nanoparticle For Targeted Pancreatic Cancer Therapy	Yang, Lily	Emory University
U01CA199235	Identification Of Synthetic Lethal Interactors In Pancreatic Cancer	Der, Channing J.	University of North Carolina at Chapel Hill
U01CA202241	ECM Geometrical And Mechanical Properties Modulate RTK Signaling	Groves, Jay T.	University of California, Berkeley
U54CA151668	Texas Center For Cancer Nanomedicine	Cristini, Vittorio	University of Texas Health Science Center at Houston
U54CA151838	Center Of Cancer Nanotechnology Excellence At Johns Hopkins	Searson, Peter C.	Johns Hopkins University
U54CA151880	Nanomaterials For Cancer Diagnostics And Therapeutics	Mirkin, Chad A.	Northwestern University at Chicago
U54CA151881	Center For Translational Cancer Nanomedicine	Torchilin, Vladimir P.	Northeastern University
U54CA163111	Myofibroblasts In Gastrointestinal Cancers	Wang, Timothy Cragin	Columbia University Irving Medical Center
U54CA163120	Pancreatic Tumor Micro-Environment Network	Batra, Surinder K.	University of Nebraska Medical Center

Project Number	Title	Contact PI	Institution
UH2CA191284	Leveraging Gxe Interaction To Understand Pancreatic Cancer And Altered Metabolism	Kraft, Peter	Harvard School of Public Health
UM1CA183727	Tennessee Valley Cooperative Human Tissue Network	Washington, Mary Kay	Vanderbilt University
ZIABC010451	Carbohydrate Antigen-Bearing Nanoparticles For Antitumor Therapy	Barchi, Joseph	NCI
ZIABC010774	T Cell Alternative P38 Activation Pathway	Ashwell, Jonathan	NCI
ZIABC011162	Integrative Molecular Profiling Of Human Pancreatic Cancer	Hussain, S. Perwez	NCI
ZIABC011185	Role Of Immune And Inflammation Mediators In Progression Of Pancreatic Cancer	Hussain, S. Perwez	NCI
ZIABC011267	Preclinical Drug Development In Pancreatic Cancer	Rudloff, Udo	NCI
ZIABC011343	Clinical Protocols For The Treatment Of Gastrointestinal Cancer	Greten, Tim	NCI
ZIABC011344	Immune Suppressor Mechanisms In Patients With GI Cancer	Greten, Tim	NCI
ZIABC011463	Adoption And Retooling Of GEM Model For Pancreatic Cancer	Van Dyke, Terry	NCI
ZIABC011485	Forkhead-Box (FOX) Transcription Factors In The Progression Of Pancreatic Cancer	Hussain, S. Perwez	NCI

Project Number	Title	Contact PI	Institution
ZIABC011513	Cancer-Cell Specific Therapy: Photo-Immunotherapy	Kobayashi, Hisataka	NCI
ZIABC011526	Therapeutic Evaluation In GEM Pancreatic Model	Van Dyke, Terry	NCI
ZIABC011652	Mesothelin-Targeted Immunotoxins In Pancreatic Cancer	Alewine, Christine	NCI
ZIDBC011540	Thoracic And Gastrointestinal Oncology Branch Medical Clinical Core	Hassan, Raffit	NCI
ZIEBC011653	Clinical Support	Alewine, Christine	NCI
261201200013I-0-26100010-1	Preclinical Efficacy And Intermediate Endpoint Biomarkers. Task Order Title: Preclinical Studies To Evaluate The Combination Of Metformin And As	Rao, Chinthalapally	State of Oklahoma:1109502
261201200020I-0-26100006-1	Base Contract Title: Preclinical In Vitro And In Vivo Agent Development Assays, Task Order Title: Targeting Cck2r For Pancreatic Cancer Prevention, Period Of Performance August 26, 2014 Thru August 2	Rao, Chinthalapally	State of Oklahoma:1109502
261201300060C-4-0-1	SBIR Phase I Topic 324: Development Of An Imaging Agent Targeting Sialyl Lewis A	Scholz, Wolfgang	MabVax Therapeutics Holdings, Inc.
261201400003C-0-0-1	OTHER FUNCTION- IND Enabling Development Of Nanogmp: Targeted	Li, Jun	Qualiber, Inc.
261201400047C-0-0-1	SBIR Phase II- Topic 307: Engineered Immunopet Tracers For Pancreatic Cancer	Zhang, Green	ImaginAb, Inc.

Project Number	Title	Contact PI	Institution
F30HL117546	Microparticle Docking In Pancreatic Cancer Induced VTE	Geddings, Julia E.	University of North Carolina at Chapel Hill
F32EB018715	Contrast-Enhanced Intravascular Ultrasound Imaging Of Vascular Invasion	Lindsey, Brooks D.	University of North Carolina at Chapel Hill
G13LM010912	Implementation Of A Pancreas Knowledgebase	Williams, John A.	University of Michigan
K01AA019996	Mediators Of Pancreatic Cancer Induction By Alcoholic Pancreatitis And Smoking	Edderkaoui, Mouad	Cedars-Sinai Medical Center
K08DK088945	Dissecting Stromal-Epithelial Interactions In The Adult Exocrine Pancreas	Rhim, Andrew D.	University of Michigan
K08DK105326	The Role Of Nr5a2 In Pancreas Development And Disease	Nissim, Sahar	Brigham and Women's Hospital
K08EB012859	Validation Of MRI Microvascular Biomarkers In Pancreatic Cancer With Magnetic Nanoparticles	Guimaraes, Alexander Savio Ramos	Oregon Health & Science University
P20GM103480	Nebraska Center for Nanomedicine	Bronich, Tatiana K.	University of Nebraska Medical Center
P50AA11999	Southern California Research Center for ALPD and Cirrhosis	Tsukamoto, Hidekazu	University of Southern California
R01AI058072	Structural Basis For Chemokine Function	Volkman, Brian F.	Medical College of Wisconsin
R01AT007448	Oxidative Stress And Programmed Death Pathways: Cross Talk In Pancreatic Cancer	Kumar, Addanki Pratap	University of Texas Health Science Center at San Antonio
R01DK052913	The Role Of Zinc Finger Cofactors In Pancreatic Cell Growth	Urrutia, Raul A.	Mayo Clinic, Rochester

Project Number	Title	Contact PI	Institution
R01DK055489	Pancreas Transcription Factors And Disease Model Systems	Konieczny, Stephen F.	Purdue University
R01DK060694	The Prrx-1 Transcription Factor In Pancreatic Ductal Biology	Rustgi, Anil K.	University of Pennsylvania
R01DK061220	Transcriptional Regulators Of The Exocrine Pancreatic Phenotype	MacDonald, Raymond J.	University of Texas Southwestern Medical Center
R01DK070888	Acinar Biology And Pancreatic Disease	Groblewski, Guy E.	University of Wisconsin–Madison
R01DK106266	Development, Cellular Plasticity And Homeostasis Of The Exocrine Pancreas	Sosa-Pineda, Beatriz	Northwestern University at Chicago
R01EB002568	High-Performance High-Field Parallel Mri.	Sodickson, Daniel K.	New York University School of Medicine
R01EB017270	Light-Triggered Drug Release In Primed Pancreatic Tumors	Lovell, Jonathan F.	State University of New York at Buffalo
R01EB017853	Polymeric Nanomedicines Of Small Molecules And Mirna For Treating Pancreatic Canc	Mahato, Ram I.	University of Nebraska Medical Center
R01GM076186	Chromosome Inverted Fusions, Dicentrics And Genome Instability	Weinert, Ted A.	University of Arizona
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.	University of Nebraska Medical Center

Project Number	Title	Contact PI	Institution
R13AA020691	International Symposium On Alpd And Cirrhosis	Tsukamoto, Hidekazu	University of Southern California
R13DK103527	Pancreasfest 2014: Risks And Mechanisms Of Pancreatitis And Pancreatic Diabetes	Whitcomb, David Clement	University of Pittsburgh
R13DK106939	2015 Pancreatic Diseases Gordon Research Conference	Simeone, Diane M.	Gordon Research Conferences
R13DK107248	Pancreasfest 2015: Applying Research Discoveries In Pancreatitis & Pancreatic Cancer To Patient-Centered Care	Whitcomb, David Clement	University of Pittsburgh
R15DE022902	Exploring The Role Of Wdr68 In Craniofacial Development In Zebrafish	Nissen, Robert M.	California State University, Los Angeles
R21EB017317	Solid-Phase Platform For The Preparation Of Dual-Receptor Targeted Pet Agents	Zeng, Dexing	University of Pittsburgh
R21EB018537	Eus-Guided Optoelectronic Microprobe For Accurate Pancreatic Neoplasia Diagnosis	Mycek, Mary-Ann	University of Michigan
R21EB020737	Novel Platform To Achieve High Avidity Of Heterodimers For Targeted Cancer Imaging	Zeng, Dexing	University of Pittsburgh
R21ES025839	Cytosolic Ah Receptor: Mechanism Of Action	Safe, Stephen H.	Texas A&M AgriLife Research
R41AA024029	A New Microrna-1291 Replacement Therapy For Pancreatic Cancer Disease	Bader, Andreas G.	Mirna Therapeutics, Inc.
R56AG016379	Ras Induced Senescence And Tumor Suppression	Lowe, Scott W.	Sloan-Kettering Institute

Project Number	Title	Contact PI	Institution
U01DK108288	The Exocrine And Endocrine Pancreas In Type 2 Diabetes, Pancreatitis And Cancer	Chari, Suresh T.	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	Stanford University
U01DK108306	Consortium For The Study Of Pancreatitis: Pittsburgh Clinical Center	Whitcomb, David Clement	University of Pittsburgh
U01DK108314	Pathophysiology, Epidemiology, And Prevention Of Pancreatogenic Diabetes	Pandol, Stephen J.	Cedars-Sinai Medical Center
U01DK108320	U01-Consortium For The Study Of Chronic Pancreatitis, Diabetes And Pancreatic Cancer Clinical Centers	Forsmark, Christopher E.	University of Florida
U01DK108323	Indiana University (IU) Clinical Center For Chronic Pancreatitis Clinical Research Network	Fogel, Evan	Indiana University–Purdue University 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	Ohio State University
U01DK108328	Consortium For The Study Of Chronic Pancreatitis, Diabetes And Pancreatic Cancer: Coordinating And Data	Feng, Ziding	University of Texas MD Anderson Cancer Center

Project Number	Title	Contact PI	Institution
	Management Center (CSCPDPC-CDMC)		
U01DK108332	Chronic Pancreatitis, Diabetes And Pancreatic Cancer: A Prospective Approach	Van Den Eeden, Stephen K.	Kaiser Foundation Research Institute

FY 2014 and 2015 NCI Grants Related to Small Cell Lung Cancer

Project Number	Title	Contact PI	Institution
F32CA165856	Understanding the role of SKP2 in small cell lung cancer progression	Nicolay, Brandon	Massachusetts General Hospital
K23CA164015	Novel systemic therapy to improve clinical outcome in small cell lung cancer	Owonikoko, Taofeek K.	Emory University
P50CA058187	SPORE in Lung Cancer	Bunn, Paul	University of Colorado Denver
R01CA112557	Molecular Mechanisms of Nickel-induced Tumorigenicity.	Huang, Chuanshu	New York University School of Medicine
R01CA136534	Structure-based anti-cancer drug development	Deng, Xingming	Emory University
R01CA138759	Stat3 Downstream Genes as Lung Adenocarcinoma Biomarkers	Yan, Cong	Indiana University–Purdue University Indianapolis
R01CA148867	Using mouse models to understand retinoblastoma initiation and progression	MacPherson, David	Fred Hutchinson Cancer Research Center
R01CA152316	Discovery of novel PCFT-targeted agents	Matherly, Larry H.	Wayne State University

Project Number	Title	Contact PI	Institution
R21CA169979	ACTIVITY-BASED KINASE DISCOVERY IN SMALL CELL LUNG CANCER	Haura, Eric B.	H. Lee Moffitt Cancer Center & Research Institute
R01CA170386	Novel Pathogen Associated Cancers (PQ12)	Galloway, Denise A.	Fred Hutchinson Cancer Research Center
R01CA181449	Interrogation of MLL2 as a tumor suppressor gene in lung cancer	MacPherson, David	Fred Hutchinson Cancer Research Center
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
R03CA195253	Genomic and transcriptomic characterization of atypical carcinoids of the lung	McKay, James Dowling	International Agency for Research on Cancer
R43CA177025	Synergy between MAG-1 and Cyclophosphamide for Treatment of Recurrent SCLC	Pang, Roy H.L.	Woomera Therapeutics, Inc.
R44CA174074	Development of GZ38-1, a Novel Protectant of Chemotherapy-Induced Myelosuppressio	Strum, Jay Copeland	G1 Therapeutics, Inc.
U01CA151452	Combinatorial-Designed Nano-Platforms to Overcome Tumor Drug Resistance	Amiji, Mansoor M.	Northeastern University
U54CA151838	Center of Cancer Nanotechnology Excellence at Johns Hopkins	Searson, Peter C.	Johns Hopkins University
U54CA151881	Center for Translational Cancer Nanomedicine	Torchilin, Vladimir P.	Northeastern University

Project Number	Title	Contact PI	Institution
ZIABC010448	Genetic Alterations in Lung Cancer	Wiest, Jonathan Scott	National Cancer Institute
ZIABC011418	Modulating Cancer Stem Cell Signaling in Thoracic Malignancies	Schrump, David	National Cancer Institute
ZIABC011662	Gene Expression Relationships in Human Cancer Tissues and Cell Lines	Kohn, Kurt	National Cancer Institute
ZIASC000167	Molecular Pathology of Pulmonary Carcinogenesis	Linnoila, Ilona	National Cancer Institute
ZIABC010621	Translational Studies of the Histone Deacetylase Inhibitor Romidepsin	Bates, Susan	National Cancer Institute
ZIABC011492	Biomarkers in cancer diagnosis; prognosis; and therapeutic outcome	Harris, Curtis	National Cancer Institute
ZIDBC01154	Thoracic and Gastrointestinal Oncology Branch Medical Clinical Core	Hassan, Raffit	National Cancer Institute
261201500070C-0-0-1	IGF::OT::IGF Small Business Innovation Research Program (SBIR)	Crosswell, Hal	KIYATEC, LLC
R01GM079719	Enabling new translational discoveries using a genomic data-driven nosology	Butte, Atul J.	Stanford University
R21AG042894	Translational meta-analysis for elderly lung cancer patients	Wang, Xiaofei	Duke University
R21AG047175	Comparative Effectiveness of Treatment Regimens in Lung Cancer	Lamont, Elizabeth B.	Harvard Medical School

Project Number	Title	Contact PI	Institution
R01HL115207	The lineage and function of neuroendocrine cells in lung homeostasis and injury	Chuang, Pao-Tien	University of California, San Francisco

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.

Research Area (Dollars in Millions)	FY 2014 Actual	FY 2015 Actual
Auditory System[1458]	$261	$258
Otitis Media	$16	$15
Brain Disorders	$3,894	$3,916
ALS	$48	$49
Alzheimer's Disease	$562	$589
Aphasia	$24	$25
Autism	$188	$208
Batten Disease	$5	$5
Brain Cancer	$289	$298
Cerebral Palsy	$21	$20
Epilepsy	$154	$138
Frontotemporal Dementia	$37	$36
Pick's Disease	$4	$2

[1458] The amounts cited for Auditory System; Endocrine System; Immune System; Integumentary System; Musculoskeletal System; Skeletal Muscle (former name: Muscular System); Joint, Ligaments, and Connective Tissues; and Reproductive System are not designated as official NIH RCDC, because the figures were not compiled using the standard RCDC reporting method. As result, these unofficial categories are not listed on the NIH RePORT website.

Research Area (Dollars in Millions)	FY 2014 Actual	FY 2015 Actual
Huntington's Disease	$50	$39
Injury - Traumatic brain injury	$87	$93
Intellectual and Developmental Disabilities[1459]	$355	$382
Autism	$188	$208
Down Syndrome	$18	$24
Fragile X Syndrome	$36	$38
Fetal Alcohol Syndrome	$34	$32
Multiple Sclerosis	$102	$94
Parkinson's Disease	$139	$146
Rett Syndrome	$12	$12
Reye's Syndrome	$0	$0
Schizophrenia	$253	$241
Tourette Syndrome	$4	$5
Tuberous Sclerosis	$24	$21
Cancer	$5,392	$5,389
Brain Cancer	$289	$298
Breast Cancer	$682	$674
Cervical Cancer	$116	$99
Childhood Leukemia	$105	$155
Colorectal Cancer	$271	$309
HPV and/or Cervical Cancer Vaccine	$38	$31
Liver Cancer	$74	$85
Lung Cancer	$254	$349

[1459] In FY 2015, the RCDC Mental Retardation category title was changed to Intellectual and Developmental Disabilities. Refer to footnote 15 below the category funding amount summary table displayed on the NIH RePORT website.

Research Area (Dollars in Millions)	FY 2014 Actual	FY 2015 Actual
Lymphoma	$251	$270
Hodgkin's Disease	$14	$16
Neuroblastoma	$37	$32
Ovarian Cancer	$131	$118
Pancreatic Cancer	$123	$174
Prostate Cancer	$254	$288
Uterine Cancer	$57	$52
Cardiovascular	$1,950	$1,991
Atherosclerosis	$375	$386
Heart Disease	$1,224	$1,262
Coronary Heart Disease	$421	$426
Hypertension	$216	$214
Chronic Fatigue Syndrome	$5	$6
Dental/Oral and Craniofacial Disease	$483	$493
Temporomandibular Muscle/Joint Disorder	$18	$16
Diabetes	$1,011	$1,010
Digestive Diseases	$1,607	$1,684
Digestive Diseases (Gallbladder)	$9	$8
Digestive Diseases (Peptic Ulcer)	$15	$16
Inflammatory Bowel Disease	$125	$128
Crohn's Disease	$65	$66
Colorectal Cancer	$271	$309
Liver Diseases	$605	$616
Chronic Liver Disease and Cirrhosis	$293	$295
Liver Cancer	$74	$85

Research Area (Dollars in Millions)	FY 2014 Actual	FY 2015 Actual
Hepatitis	$251	$262
Hepatitis A	$3	$4
Hepatitis B	$48	$42
Hepatitis C	$111	$96
Endocrine System[1458]	$1,864	$1,849
Estrogen	$203	$194
Diethylstilbestrol	$1	$1
Eye Disease and Disorders of Vision	$824	$779
Macular Degeneration	$82	$82
Hematology	$1,189	$1,217
Childhood Leukemia	$105	$155
Cooley's Anemia	$18	$15
Septicemia	$100	$103
Sickle Cell Disease	$75	$75
Immune System[1458]	$5,132	$5,179
Allergic Rhinitis (Hay Fever)	$6	$5
Asthma	$241	$281
Autoimmune Disease	$822	$821
Inflammatory Bowel Disease	$125	$128
Lupus	$99	$90
Multiple Sclerosis	$102	$94
Myasthenia Gravis	$8	$7
Psoriasis	$13	$14
Scleroderma	$24	$22
Childhood Leukemia	$105	$155

Research Area (Dollars in Millions)	FY 2014 Actual	FY 2015 Actual
Food Allergies	$35	$39
Lymphoma	$251	$270
Hodgkin's Disease	$14	$16
Vaccine Related	$1,573	$1,585
HPV and/or Cervical Cancer Vaccine	$38	$31
Malaria Vaccine	$36	$44
Vaccine Related (AIDS)	$533	$541
Biodefense	$1,746	$1,736
Tuberculosis Vaccine	$31	$23
Integumentary System[1458]	$357	$402
Psoriasis	$13	$14
Scleroderma	$24	$22
Kidney and Urologic Diseases[1454]	$1,050	$1,096
Kidney Disease	$549	$564
Polycystic Kidney Disease	$36	$29
Urologic Diseases	$494	$527
Interstitial Cystitis	$9	$10
Prostate Cancer	$254	$288
Lung	$1,329	$1,619
Acute Respiratory Distress Syndrome	$85	$108
Asthma	$241	$281
Chronic Obstructive Pulmonary Disease	$107	$97
Cystic Fibrosis	$77	$80
Emphysema	$27	$28
Lung Cancer	$254	$359

Research Area (Dollars in Millions)	FY 2014 Actual	FY 2015 Actual
Perinatal/Neonatal Respiratory Distress Syndrome	$52	$31
Pneumonia	$107	$112
Mental Health	$2,213	$2,263
Autism	$188	$208
Attention Deficit Disorder	$44	$41
Depression	$396	$390
Schizophrenia	$253	$241
Musculoskeletal System[1458]	$1,130	$1,134
Skeletal Muscle[1458]	$450	$446
Muscular Dystrophy	$78	$77
Myotonic Dystrophy	$9	$9
Duchenne/Becker Muscular Dystrophy	$32	$30
Facioscapulohumeral Muscular Dystrophy	$7	$8
Myasthenia Gravis	$8	$7
Spinal Muscular Atrophy	$16	$11
Skeletal System[1458]	$523	$508
Osteogenesis Imperfecta	$11	$11
Osteoporosis	$141	$146
Paget's Disease	$0	$1
Joints, Ligaments, and Connective Tissues[1458]	$446	$454
Temporomandibular Muscle/Joint Disorder	$18	$16
Neurosciences	$5,580	$5,742
Pain Research[1458]	$499	$463
Fibromyalgia	$10	$8
Headaches	$24	$24

Research Area (Dollars in Millions)	FY 2014 Actual	FY 2015 Actual
Migraines	$20	$20
Pain Conditions—Chronic	$402	$391
Vulvodynia	$3	$2
Reproductive System[1458]	$1,071	$1,128
Cervical Cancer	$116	$99
Ovarian Cancer	$131	$118
Prostate Cancer	$254	$288
Uterine Cancer	$57	$52
Vulvodynia	$3	$2
Adolescent Sexual Activity	$68	$85
Teenage Pregnancy	$16	$14
Contraception/Reproduction	$394	$424
Endometriosis	$7	$10
Fibroid Tumors (Uterine)	$9	$10
Infertility	$76	$72

Appendix J:
Acronyms

Acronym	Meaning
2DG	2-deoxyglucose
3D	three-dimensional
15-PGDH	15-hydroxyprostaglandin dehydrogenase
A3A	APOBEC3A
A4	Anti-Amyloid Treatment in Asymptomatic Alzheimer's
AA	alopecia areata
AAV	ANCA-associated vasculitis
ABCD	Adolescent Brain Cognitive Development
ABI	auditory brainstem implant
ACC	Autism Coordinating Committee
ACD	Advisory Committee to the Director
ACE	Autism Centers of Excellence
ACGME	Accreditation Council for Graduate Medical Education
ACL	anterior cruciate ligament
ACS	American Cancer Society
ACT	adoptive T-cell therapy
AD	Alzheimer's disease
ADAGES	African Descent and Glaucoma Evaluation Study
ADAPT	Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking
ADCs	Alzheimer's Disease Centers
ADCS	Alzheimer's Disease Cooperative Study
ADDM	Autism and Developmental Disabilities Monitoring
ADGC	Alzheimer's Disease Genetics Consortium
ADHD	attention deficit hyperactivity disorder
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADPKD	autosomal dominant polycystic kidney disease
ADRD	Alzheimer's disease–related dementias
ADSP	Alzheimer's Disease Sequencing Project
AEIO	Autism Evaluation Implementation Oversight
AGI	Audacious Goals Initiative
AHRQ	Agency for Healthcare Research and Quality
AI/AN	American Indian/Alaska Native
AIDS	acquired immunodeficiency syndrome
ALF	acute liver failure
ALFSG	Acute Liver Failure Study Group

Acronym	Meaning
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
AMD	age-related macular degeneration
AMP	Accelerating Medicines Partnership
AMPATH	Academic Model Providing Access to Healthcare
AMP-T2D	Accelerating Medicines Partnership Type 2 Diabetes
AMR	antimicrobial resistance
ANCA	antineutrophil cytoplasmic autoantibodies
ANCHOR	Anal Cancer High Grade Squamous Intraepithelial Lesion Outcomes Research
API	application programming interface
API ADAD	Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease
API APOE4	Alzheimer's Prevention Initiative apolipoprotein E
APOE4	apolipoprotein E
ARID	Accelerating Research on Intervertebral Disc
ART	antiretroviral therapy
ARV	antiretroviral
ASD	autism spectrum disorder
ASP	Anticonvulsant Screening Program
a-tDCS	anodal transcranial direct current stimulation
aSLE	adult-onset systemic lupus erythematosus
AUD	alcohol use disorder
BARD	Best African American Response to Asthma Drugs
BARDA	Biomedical Advanced Research and Development Authority
BBDC	Brittle Bone Disorders Consortium
BCBC	Beta Cell Biology Consortium
BCSC	Breast Cancer Surveillance Consortium
BD2K	Big Data to Knowledge
BDNF	brain-derived neurotrophic factor
BE	Barrett's esophagus
BEMT	Biobank Economics Modeling Tool
BEST	Broadening Experiences in Scientific Training
BETRNet	Barrett's Esophagus Translational Research Network
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BLSA	Baltimore Longitudinal Study of Aging
BMD	bone mineral density
BMI	body mass index
BMS	bone material strength
bNAb	broadly neutralizing antibody
BNST	bed nucleus of the stria terminalis
BPA	bisphenol A
BPCA	Best Pharmaceuticals for Children Act
BPN	Blueprint Neurotherapeutics Network

Acronym	Meaning
BPV	Biospecimen Pre-analytical Variables
BRAIN	Brain Research through Advancing Innovative Neurotechnologies®
BRCs	Bioinformatics Resource Centers for Infectious Diseases
BRD	Biospecimen Research Database
BriDGs	Bridging Interventional Development Gaps
BRN	Biospecimen Research Network
BUILD	Building Infrastructure Leading to Diversity
B-WELL-Mom	Breathe-Wellbeing, Environment, Lifestyle and Lung Function
CADET II	Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases II
CAR	chimeric antigen receptor
CARES	Autism Collaboration, Accountability, Research, Education, and Support
CAS	carotid artery stenosis
CC	NIH Clinical Center
CCEH	Children's Environmental Health and Disease Prevention
CCITLA	Cancer Clinical Oncology Team Leadership Awards
CCLF	Cancer Control Leadership Forum
CDC	Centers for Disease Control and Prevention
CDR	Comprehensive Data Resource
CEC	Coordination and Evaluation Center
CECTR	Center for Evaluation and Coordination of Training and Research
CEIRS	Centers of Excellence for Influenza Research and Surveillance
CF	cystic fibrosis
CFH	complement factor H
CFS	chronic fatigue syndrome
CGD	chronic granulomatous disease
CGH	Center for Global Health
CHARGE	Childhood Autism Risks from Genetics and the Environment
CHD	coronary heart disease
ChiLDReN	Childhood Liver Disease Research Network
CID	combined immunodeficiency
CISNET	Cancer Intervention and Surveillance Modeling Network
CIT	Center for Information Technology
CJD	Creutzfeldt-Jakob disease
CJ-DATS	Criminal Justice Drug Abuse Treatment Studies
CKD	chronic kidney disease
CKiD	Chronic Kidney Disease in Children Study
cLBP	chronic low-back pain
CMDs	congenital muscular dystrophies
CNCC	Chinese National Cancer Center
CNV	choroidal neovascularization
COE	Center of Excellence

Acronym	Meaning
CoEPEs	Centers of Excellence for Pain Education
CollegeAIM	College Alcohol Intervention Matrix
COPD	chronic obstructive pulmonary disease
COPE	Creating Opportunities for Personal Empowerment
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CPEA	Collaborative Programs of Excellence in Autism
CPI	Community Priority Index
CPTAC	Clinical Proteomic Tumor Analysis Consortium
CRAN	Collaborative Research on Addiction at NIH
CRF	corticotropin-releasing factor
CRIC	Chronic Renal Insufficiency Cohort Study
CRISPR	clustered regularly interspaced short palindromic repeats
CSBC	Cancer Systems Biology Consortium
CSF	cerebrospinal fluid
cSLE	childhood-onset systemic lupus erythematosus
CSR	Center for Scientific Review
CT	computed tomography
CTCs	circulating tumor cells
ctDNA	circulating tumor DNA
CTE	chronic traumatic encephalopathy
CTL	cytotoxic T lymphocyte
CTP	Center for Tobacco Products
CTSA	Clinical and Translational Science Awards
CTSA ACT	Clinical and Translational Science Awards Accrual to Clinical Trials
CVD	cardiovascular disease
CWOW	Epilepsy Centers Without Walls
D&I	dissemination and implementation
D2d	Vitamin D and type 2 Diabetes
DA	dopamine
DALY	disability-adjusted life year
DARPA	Defense Advanced Research Projects Agency
dATP	deoxyadenosine triphosphate
dbGaP	database of Genotypes and Phenotypes
DC	dyskeratosis congenita
DCCT	Diabetes Control and Complications Trial
DEBUT	Design by Biomedical Undergraduate Teams
DHA	docosahexaenoic acid
DIAN-TU	Dominantly Inherited Alzheimer's Network Trials Unit
DISC1	Disrupted in Schizophrenia-1
DLBCL	diffuse large B-cell lymphoma
DMCC	Data Management and Coordinating Center

Acronym	Meaning
DMD	Duchenne muscular dystrophy
DOC	dental, oral, and craniofacial
DOCTRC	DOC Tissue Regeneration Consortium
DoD	Department of Defense
DPC	Diversity Program Consortium
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DPPOS	Diabetes Prevention Program Outcomes Study
DS	Down syndrome
DSLD	Dietary Supplement Label Database
DXA	dual-energy X-ray absorptiometry
EAC	esophageal adenocarcinoma
EALs	early adverse life events
EARLI	Early Autism Risk Longitudinal Investigation
EB	epidermolysis bullosa
EBV	Epstein-Barr virus
ECGs	electrocardiographies
ECHO	Environmental Influences on Child Health Outcomes Program
ECs	endothelial cells
EDIC	Epidemiology of Diabetes Interventions and Complications Study
EDRN	Early Detection Research Network
ED-STARS	Emergency Department Screen for Teens at Risk for Suicide
EHR	electronic health record
eMERGE	Electronic Medical Records and Genomics
ENCODE	ENCyclopedia Of DNA Elements
ENDURE	Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences
EoE	eosinophilic esophagitis
EPA	Environmental Protection Agency
EPCs	endothelial progenitor cells
eRA	electronic Research Administration
ESRD	end-stage renal disease
ETSP	Epilepsy Therapy Screening Program
EVD	Ebola virus disease
exRNA	extracellular RNA
FAES	Foundation for Advanced Education in the Sciences
FAST	Fast-Fail Trials
FAST-AS	Fast-Fail Trials-Autism Spectrum Disorders
FAST-MAS	Fast-Fail Trials-Mood and Anxiety Spectrum Disorders
FAST-PS	Fast-Fail Trials-Psychotic Spectrum Disorders
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDAMA	Food and Drug Administration Modernization Act of 1997

Acronym	Meaning
FIC	Fogarty International Center
FITBIR	Federal Interagency Traumatic Brain Injury Research
FLINT	Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment
FLS	fibroblast-like synoviocytes
fMRI	functional magnetic resonance imaging
FNIH	Foundation for the National Institutes of Health
FOAs	Funding Opportunity Announcements
FORCE11	The Future of Research Communications and e-Scholarships Community
FSHD	facioscapulohumeral muscular dystrophy
FSPTCA	Family Smoking Prevention and Tobacco Control Act
FTD	frontotemporal dementia
FUS	Follow-Up Study
FXTAS	fragile X-associated tremor/ataxia syndrome
FY	fiscal year
GA	geographic atrophy
GAL	galanin
GCPM	Global Cancer Project Map
GDM	gestational diabetes mellitus
GDS	NIH Genomic Data Sharing
GeM-HD	Genetic Modifiers of Huntington's Disease
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
GPRA	Government Performance and Results Act
GRADE	Glycemia Reduction Approaches in Diabetes: An Effectiveness Study
GRHL3	grainyhead-like 3
GSIG	GeroScience Interest Group
GTEx	Genotype-Tissue Expression
GTR	Genetic Testing Registry
GUDID	Global Unique Device Identifier Database
GUDMAP	GenitoUrinary Development Molecular Anatomy Project
GVHD	Graft-versus-host disease
GVIRF	Global Vaccine and Immunization Research Forum
GWAS	genome-wide association studies
HA	hemagglutinin
HAPO	Hyperglycemic and Adverse Pregnancy Outcome
HBV	hepatitis B virus
HCAP	Harmonized Cognitive Assessment Protocol
HCP	Human Connectome Project
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HD	Huntington's disease

Acronym	Meaning
HDI	Human Development Index
HDV	hepatitis D virus
HERCULES	Emory Health and Exposome Research Center: Understanding Lifetime Exposures
HERV-K	human endogenous retrovirus-K
HES	hypereosinophilic syndromes
HEUS	hypereosinophilia of unknown significance
HGPS	Hutchinson-Gilford progeria syndrome
HH	Hoyeraal-Hreidarsson
HHS	U.S. Department of Health and Human Services
HIRN	Human Islet Research Network
HIV	human immunodeficiency virus
HIV-STIC	HIV Services and Treatment Implementation in Corrections
HLA	human leukocyte antigen
HMP	Human Microbiome Project
HNSCC	head and neck squamous cell carcinoma
HOPE	HIV Organ Policy Equity
HPV	human papillomavirus
HRS	Health and Retirement Study
HSIL	High Grade Squamous Intraepithelial Lesion
HSR	health services research
HSRProj	Health Services Research Projects
HSRR	Health Services and Sciences Research Resources
IACC	Interagency Autism Coordinating Committee
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBSOS	IBS Outcome Study
IC/BPS	Interstitial cystitis/bladder pain syndrome
ICBP	Integrative Cancer Biology Program
ICs	Institutes and Centers
ICT	information and communication technology
IDeA	Institutional Development Award
IDEAL	Impact of Diet, Exercise, and Lifestyle on Fertility
IeDEA	International Epidemiological Databases to Evaluate AIDS
IDH1	isocitrate dehydrogenases
IFN	interferon
IgA	immunoglobulin A
IgAN	immunoglobulin A nephropathy
IIH	Idiopathic Intracranial hypertension
IL	interleukin
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
INCL	infant neuronal ceroid lipofuscinosis

Acronym	Meaning
IND	Investigational New Drug
IOP	intraocular pressure
IPPCR	Introduction to the Principles of Practice of Clinical Research
iPS	induced pluripotent stem
iPSC	Induced pluripotent stem cell
IRACDA	Institutional Research and Academic Career Development Awards
IRB	institutional review board
IRBIT	inositol 1,4,5-trisphosphate
IRP	Intramural Research Program
ISEF	Intel International Science and Engineering Fair
ISFP	Iowa Strengthening Families Program
ITP	Interventions Testing Program
JJ-TRIALS	Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System
KS	Kaposi sarcoma
LABS	Longitudinal Assessment of Bariatric Surgery
LAD-I	leukocyte adhesion deficiency type I
LAM	lymphangioleiomyomatosis
LASV	Lassa Virus
LCP	Lifespan Connectome Project
LDGs	low-density granulocytes
LDM	long-distance migration
LEAP	Learning Early About Peanut Allergy
LGBT	Lesbian, Gay, Bisexual, and Transgender
LGMDs	limb-girdle muscular dystrophies
LIFE	Lifestyle Interventions and Independence for Elders
LMIC	low- and middle-income country
LRBA	Lipopolysaccharide-responsive and beige-like anchor protein
LTL	leukocyte telomere length
LURN	Lower Urinary Tract Dysfunction Research Network
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
MACS	Multicenter AIDS Cohort Study
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MARC	Maximizing Access to Research Careers
MAT	medication-assisted treatment
MATICCE	Medication-Assisted Treatment Implementation in Community Correctional Environments
MBTS	modified Blalock-Taussig shunt
MCI	mild cognitive impairment
MD	muscular dystrophy

Acronym	Meaning
MD-CARE Act	Muscular Dystrophy Community Assistance, Research, and Education Amendments
MDCRC	Muscular Dystrophy Cooperative Research Centers
MDR-TB	multidrug-resistant tuberculosis
MDSCs	myeloid-derived suppressor cells
ME	myalgic encephalomyelitis
MECP2	methyl CpG binding protein 2
MERS-CoV	Middle East respiratory system coronavirus
MHBG	Mental Health Block Grant
MILES	Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus
MIM	Mentoring In Medicine
MIMIC-III	Medical Information Mart for Intensive Care III
MMA	monomethylarsonate
MoTrPAC	Molecular Transducers of Physical Activity Consortium
MoU	memorandum of understanding
MR	magnetic resonance
MRD	minimal residual disease
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRSA	methicillin-resistant *Staphylococcus Aureus*
MS	multiple sclerosis
MSCs	mesenchymal stem cells
MSM	men who have sex with men
MSSA	methicillin-susceptible *Staphylococcus Aureus*
MSTP	Medical Scientist Training Program
MTCT	mother-to-child transmission
MTF	Monitoring the Future
mTOR	mechanistic target of rapamycin
MUC1	mucin 1
NAACCR	North American Association of Central Cancer Registries
NACC	National Alzheimer's Coordinating Center
NAFLD	nonalcoholic fatty liver disease
NAPA	National Alzheimer's Project Act
NASA	National Aeronautics and Space Administration
NBSTRN	Newborn Screening Translational Research Network
NCANDA	National Consortium on Alcohol and Neurodevelopment in Adolescence
NCATS	National Center for Advancing Translational Sciences
NCBI	National Center for Biotechnology Information
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NCI-MATCH	NCI Molecular Analysis for Therapy Choice

Acronym	Meaning
NCIG	NIAAA Clinical Investigations Group
NCMRR	National Center on Medical Rehabilitation Research
NCRAD	National Cell Repository for Alzheimer's Disease
NDAR	National Database for Autism Research
NDCT	National Database for Clinical Trials Related to Mental Illness
NEI	National Eye Institute
NESARC III	National Epidemiological Survey on Alcohol and Related Conditions
NETT	Neurological Emergencies Treatment Trials
NeuroNEXT	Network for Excellence in Neuroscience Clinical Trials
NF1	neurofibromin 1
NHALES	Natural History of Asthma with Longitudinal Environmental Sampling study
NHANES	National Health and Nutrition Examination Survey
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
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
NIF	Neuroscience Information Framework
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
NIST	National Institute of Standards and Technology
NITRC	Neuroimaging Informatics Tools and Resources Clearinghouse
NK	natural killer
NKT	natural killer T
NLM	National Library of Medicine
NLST	National Lung Screening Trial
NPC	Niemann-Pick disease type C
NPY	neuropeptide Y

Acronym	Meaning
NRMN	National Research Mentoring Network
NRSA	National Research Service Award
NRTIs	nucleoside reverse transcriptase inhibitors
NTU	Discovering New Therapeutic Uses
OAICs	Claude D. Pepper Older Americans Independence Centers
OAR	Office of AIDS Research
OBSSR	Office of Behavioral and Social Sciences Research
OCA	obeticholic acid
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
OIs	opportunistic infections
OIA	Outstanding Investigator Award
OIR	Office of Intramural Research
OM	otitis media
OMB	Office of Management and Budget
OMF	Oncology Models Forum
OPPERA	Orofacial Pain: Prospective Evaluation and Risk Assessment
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
OSI	optical surface imaging
OTA	Other Transaction Authority
P2P	Pathways to Prevention
PA	program announcement
PAH	polycyclic aromatic hydrocarbon
PCORI	Patient-Centered Outcomes Research Institute
PCR	polymerase chain reaction
PCRC	Palliative Care Research Cooperative
PD	Parkinson's disease
PEN	Programs of Excellence in Nanotechnology
PEPR	Patient Reported Outcomes in Chronic Diseases
PET	position emission tomography
PETAL	Prevention and Early Treatment of Acute Lung Injury
Pf	*Plasmodium falciparum*
PFS	progression-free survival
PGC	Psychiatric Genomic Consortium
PGM3	phosphoglucomutase 3
PHS	Public Health Service

Acronym	Meaning
PI3K	phosphatidylinositol 3-kinase
PICALM	phosphatidylinositol binding clathrin assembly
PLCO	Prostate, Lung, Colorectal, and Ovarian
PLUS	Prevention of Lower Urinary tract Symptoms
PM	particulate matter
PMI	Precision Medicine Initiative
POHS	preventive oral health services
PopART	Population Effects of Antiretroviral Therapy to Reduce HIV Transmission
PPA	primary progressive aphasia
PPARγ	peroxisome proliferator-activated receptor gamma
PQ	Provocative Questions
PRAT	Postdoctoral Research Associate
PREDICT-HD	PREDICT Huntington's Disease
PrEP	pre-exposure prophylaxis
PRIDE	Program to Increase Diversity Among Individuals Engaged in Health-Related Research
PRISMS	Pediatric Research Using Integrated Sensor Monitoring Systems
PROSPER	Promoting School-Community-University Partnerships to Enhance Resilience
PS-ON	Physical Sciences-Oncology Network
PTC	Pulmonary Trials Cooperative
PTCy	post-transplant high-dose cyclophosphamide
PTSD	posttraumatic stress disorder
PVDOMICS	Pulmonary Vascular Disease Phenomics
QIBA	Quantitative Imaging Biomarkers Alliance
QSP	quantitative systems pharmacology
R&D	research and development
RA	rheumatoid arthritis
RAISE	Recovery After an Initial Schizophrenia Episode
RAMPART	Rapid Anticonvulsant Medication Prior to Arrival Trial
RAPID	Rapidly-Acting Treatments for Treatment-Resistant Depression
RAPIDD	Research and Policy in Infectious Diseases Dynamics Rapid Acquisition of Pre- and Post-Incident Disaster Data
RCDC	Research, Condition, and Disease Categorization
RCT	root canal therapy
RDCRN	Rare Diseases Clinical Research Network
RDC-TMD	Research Diagnostic Criteria for Temporomandibular Disorders
RDoC	Research Domain Criteria
RDoCdb	Research Domain Criteria Database
RECRUIT	Randomized Recruitment Intervention Trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
REPRIEVE	Randomized Trial to Prevent Vascular Events in HIV

Acronym	Meaning
RFA	request for applications
RGC	retinal ganglion cell
RII	Resource Identification Initiative
RISe	Restore Insulin Secretion
RLDC	Rare Lung Diseases Consortium
RNA	ribonucleic acid
RNR	ribonucleotide reductase
ROAR	Recruiting Older Adults into Research
RPE	retinal pigment epithelium
RSV	respiratory syncytial virus
RVPAS	right ventricle-to-pulmonary artery shunt
SAA	severe aplastic anemia
SAMHSA	Substance Abuse and Mental Health Services Administration
SARS	Severe Acute Respiratory Syndrome
SBIR	Small Business Innovation Research
SCD	sickle cell disease
SCID	severe combined immunodeficiency
SCLS	systemic capillary leak syndrome
SCOR	Specialized Center of Research
SCORE	Support of Competitive Research
SEARCH	Search for Diabetes in Youth
SCTC	State and Community Tobacco Control
SEER	Surveillance, Epidemiology, and End Results
Sema3D	semaphorin 3D
SEP	socioeconomic position
SEPA	Science Education Partnership Award
SES	socioeconomic status
SGI	Summer Genetics Institute
SIREN	Strategies to Innovate Emergency Care Clinical Trials Network
SLE	systemic lupus erythematosus
SNA	spherical nucleic acid
SNIFF	Study of Nasal Insulin to Fight Forgetfulness
SNP	single nucleotide polymorphism
SOD	sphincter of Oddi dysfunction
SOP	standard operating procedure
SPARC	Stimulating Peripheral Activity to Relieve Conditions
SPF 10-14 + LST	Strengthening Families Program: For Parents and Youth 10-14 plus the school-based Life Skills Training
SPIRIT	Suicide Prevention for at-Risk Individuals in Transition
SPORE	Specialized Program for Research Excellence
SPORT	Spine Patient Outcomes Research Trial
SPRINT	Systolic Blood Pressure Intervention Trial

Acronym	Meaning
SRG	Scientific Review Group
SS	Sjögren's syndrome
SSA	Social Security Administration
SSc	systemic sclerosis
STAART	Studies to Advance Autism Research and Treatment
STAR	Supplements to Advance Research
START	Strategic Timing of Antiretroviral Therapy
STD	sexually transmitted disease
STEM	science, technology, engineering, and mathematics
STEP-UP	Short-Term Research Experience Program for Underrepresented Persons
STI	sexually transmitted infection
STTR	Small Business Technology Transfer
SUDEP	sudden unexpected death in epilepsy
SUMA	SUrface MApping
TB	tuberculosis
TBI	traumatic brain injury
TCD	transcranial Doppler
TCGA	The Cancer Genome Atlas
TEDDY	The Environmental Determinants of Diabetes in the Young
TEEN	Thinking, Emotions, Exercise, Nutrition
TGF	transforming growth factor
TGW	transgender women
Th9	T helper 9
TIL	tumor-infiltrating lymphocyte
TIME	Transgenerational Inheritance in Mammals after Environmental Exposure
TIP	targeted infection-control program
TMD	temporomandibular disorder
TMWG	Trans-NIH Microbiome Working Group
TOPMed	Trans-Omics for Precision Medicine
Tox21	Toxicology in the 21st Century
TRACK TBI	Transforming Research and Clinical Knowledge in Traumatic Brain Injury
TRAP	traffic-related air pollutants
Treg	T-regulatory cell
TRSP	Tobacco Regulatory Science Program
TSC	tuberous sclerosis complex
TSTP	Translational Science Training Program
TTS	triple trisomic
UCLA	University of California, Los Angeles
UDN	Undiagnosed Diseases Network
US	ultrasound
USAID	U.S. Agency for International Development
USDA	U.S. Department of Agriculture

Acronym	Meaning
USPSTF	U.S. Preventive Services Task Force
U-STAR	Undergraduate Student Training in Academic Research
UT	University of Texas
UTI	urinary tract infection
UUI	urgency urinary incontinence
UV	ultraviolet
VA	Department of Veterans Affairs
VIP	vasoactive intestinal peptide
VITA	Vascular Interventions/Innovations and Therapeutic Advances
VLP	virus-like particle
VOC	vaso-occlusive crisis
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
XLRS	X-linked retinoschisis
Yp	*Yersinia pseudotuberculosis*