Report of the Director
National Institutes of Health

Fiscal Years 2019 – 2021

National Institutes of Health
Turning Discovery Into Health

Report of the Director

National Institutes of Health

Fiscal Years 2019, 2020, and 2021

Preface

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

Chapter Organization

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

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

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

Chapter 2 begins with a brief introduction to the continuum of biomedical research at NIH. The research continuum moves from basic research, to preclinical translational research, to clinical research, and finally to postclinical translational research. As reflected by the last step of the continuum, NIH[2] works to ensure

[1] Section 2032 of the *21st Century Cures Act* (P.L. 114-255) amended section 403 of the *Public Health Service (PHS) Act* to change the reporting requirement from every two years to every three years. Prior to this, five NIH Biennial Reports were produced. See Appendix A of this report for language in the *PHS Act* that is relevant to this report. Previous Biennial and Triennial Reports can be found at: https://dpcpsi.nih.gov/oepr/nih-triennial-report.

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

the uptake of research results by healthcare practitioners and the public in order to bring the extensive evidence base of NIH research to clinical and community practice, ultimately turning discovery into health. The introduction is followed by a more in-depth discussion of these stages of the bench-to-practice continuum at NIH, including information on the types of activities conducted at each stage across NIH Institutes and Centers (ICs) and the Office of the Director (OD).

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

Chapter 3 presents a cross section of NIH research activities during the fiscal years (FY) 2019, 2020, and 2021 reporting period that covers the following topics:

- Cancer
- Neuroscience
- Life Stages, Human Development, and Rehabilitation
- Chronic Diseases and Organ Systems
- Autoimmune Diseases
- Infectious Diseases and Biodefense (including COVID-19)
- Public Health Emergency Preparedness
- Rare and Undiagnosed Diseases
- Microbiome
- Minority Health and Health Disparities
- Women's Health and Pregnancy Outcomes
- Emerging Technologies
- Research Resources and Infrastructure

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

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 portfolio of such centers. This chapter also provides overviews, progress reports for FY 2019, 2020, and 2021 (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:

1. Alzheimer's Disease Centers (1984)
2. Claude D. Pepper Older Americans Independence Centers of Excellence (1989)
3. Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (2001)

4. National Institute on Minority Health and Health Disparities Centers of Excellence (2001)
5. Rare Diseases Clinical Research Network (2003)
6. 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 Triennial Report and the inclusion of certain contents within it.
- Appendix B provides the Report of the Advisory Committee on Research on Women's Health.
- Appendix C provides information on actions undertaken to conduct or support research related to tickborne diseases and other vector-borne diseases.
- Appendix D provides the report of NIH Institute/Center Research Collaborations.
- Appendix E provides data on the National Research Service Award program (the primary NIH research training program), the National Library of Medicine Research Training programs, and NIH graduate medical education activities.
- Appendix F provides the NIH report, Monitoring Adherence to the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.
- Appendix G provides a catalog of biomedical information systems.
- Appendix H provides information on actions undertaken to carry out scientific frameworks on recalcitrant cancer.
- Appendix I provides NIH funding levels for chronic diseases and organ systems.
- Appendix J provides information on EUREKA Prize Competitions.
- Appendix K provides a list of acronyms that are used in this report.

Contents

Chapter 1 About NIH

Statement of the Director

It is my honor to present to Congress the Triennial Report of the Director of the National Institutes of Health (NIH) for FY 2019, 2020, and 2021. With congressional support, NIH continues to pursue its mission of discovering fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce illness and disability. On October 31, 2020, NIH marked the 80th anniversary of President Franklin Delano Roosevelt's dedication of the NIH campus in Bethesda, MD. In 1940, President Roosevelt called on NIH to use the power of science "to do infinitely more" for the health of all people with "no distinctions of race, of creed [ideology], or of color." As the largest public funder of biomedical and behavioral and social science research in the world, NIH has been the driving force behind decades of scientific and medical advances that have improved the health of people throughout the United States (U.S.) and around the globe, living up to the vision that President Roosevelt articulated over 80 years ago.

The nation faced an unprecedented national and global public health emergency when the COVID-19 pandemic emerged in 2020. NIH was able to pivot rapidly to respond to this global public health crisis while still maintaining a robust portfolio of diverse and innovative research across a broad spectrum of basic, translational, and clinical research, dealing with almost every human disease.

Driving the COVID-19 Pandemic Response

NIH's long-term and ongoing investments in fundamental science and technology development provided a strong platform to jumpstart NIH's response to the COVID-19 pandemic. NIH quickly leveraged existing research and clinical research infrastructure to develop new, flexible, processes and mechanisms to support innovative research to develop and evaluate novel medical counter measures, including diagnostics, treatments, and vaccines.

NIH launched the Rapid Acceleration of Diagnostics (RADx®) initiative to speed innovation in the development, commercialization, and implementation of technologies for SARS-CoV-2 testing, the virus that causes COVID-19.[3] The RADx initiative was launched in April 2020, just five days after Congress appropriated $1.5 billion to NIH to substantially increase the number, type, and availability of diagnostic tests. Using a shark-tank-like approach, RADx reviewed proposed technology solutions, and drove the development of accurate, fast, easy-to-use, sensitive, specific, and widely accessible diagnostic testing.[4] The RADx initiative was able to achieve this in less than six months, when historically, this process takes up to five years. RADx-funded projects included new technology development and new applications of existing technologies that make diagnostic tests easier to use, easier to access, and more reliable and accurate. In fact, the first over the counter at-home test authorized by the Food and Drug Administration

[3] https://www.nih.gov/research-training/medical-research-initiatives/radx
[4] https://directorsblog.nih.gov/tag/shark-tank/

(FDA) was developed with support from the RADx program,[5] and the program continues to support expanding the availability and accessibility of diagnostic tests.[6]

Beyond diagnostics, NIH-funded researchers quickly pivoted their research programs to investigate potential treatments for COVID-19. In April 2020, NIH launched the Accelerating COVID-19 Therapeutic Interventions and Vaccines initiative (ACTIV). ACTIV is a unique public-private partnership involving 20 biopharmaceutical companies, academic experts, and multiple federal agencies with the specific goal of developing a coordinated research strategy across each of these partners to speed the development of treatments and vaccines for COVID-19.[7] The ACTIV initiative was able to build on the strength of the public-private partnerships to respond rapidly to identify and accelerate clinical testing of the most promising vaccine candidates and potential treatments. ACTIV evaluated existing FDA-licensed medications for new use in treating COVID-19, improving clinical trial efficacy, and coordinating data sharing as new SARS-CoV-2 variants emerged. Through ACTIV, NIH funded a large clinical trial to test several existing prescription and over-the-counter medications to treat symptoms of COVID-19.[8] This research has resulted in two authorized treatments for COVID-19, Paxlovid (a combination of nirmatrelvir and ritonavir) and Lagevrio (molnupiravir), which can be taken at home, as well as a growing number of other authorized and approved treatments that can be administered in hospitals to treat severe disease.[9,10,11]

To efficiently develop safe and effective vaccines against the SARS-CoV-2 virus, NIH leveraged more than 50 years of NIH-supported research on viruses and advances in general vaccine technology.[12] Decades of NIH-funded research on mRNA as a vehicle to deliver vaccines, and ongoing development of mRNA vaccines for other viruses, including Nipah virus and Middle East Respiratory Syndrome (MERS) coronavirus, significantly contributed to the development and production of mRNA vaccines for SARS-CoV-2 at unprecedented accelerated timeframes. Additionally, NIH built on a foundation of decades of human immunodeficiency virus (HIV) research infrastructure to facilitate crucial clinical testing of potential treatments and vaccines. The COVID-19 Prevention Trials Network, a merged network of existing HIV-focused clinical trials resources was able to rapidly enroll thousands of volunteers in large-scale clinical trials to test experimental vaccines to protect people from SARS-CoV-2 and COVID-19.[13] This long-term investment in NIH biomedical research and clinical research infrastructure is what facilitated NIH's

[5] https://www.nih.gov/news-events/news-releases/nih-funded-covid-19-home-test-first-receive-over-counter-authorization-fda
[6] https://www.nih.gov/news-events/news-releases/nih-funded-pediatric-covid-19-testing-study-finds-school-aged-children-can-self-swab
[7] https://www.nih.gov/research-training/medical-research-initiatives/activ
[8] https://www.nih.gov/news-events/news-releases/large-clinical-trial-study-repurposed-drugs-treat-covid-19-symptoms
[9] https://www.nature.com/articles/d41586-022-00562-0?mc_cid=d63a9f06e0&mc_eid=96a69fdb26
[10] https://covid19.nih.gov/covid-19-topics/covid-19-treatments
[11] https://www.fda.gov/consumers/consumer-updates/know-your-treatment-options-covid-19
[12] https://covid19.nih.gov/nih-strategic-response-covid-19/decades-making-mrna-covid-19-vaccines
[13] https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trials-network-test-covid-19-vaccines-other-prevention-tools

rapid and effective response; it allowed NIH to build on existing structures to address the COVID-19 pandemic.

Investment in research and technology is insufficient if the outcomes of that research are not implemented and accepted by the communities most affected. In September 2020, NIH launched the Community Engagement Alliance (CEAL) Against COVID-19 Disparities.[14] CEAL's mission is to provide trustworthy, science-based information through active community engagement and outreach to the people most affected by the COVID-19 pandemic, with the goal of building long-lasting partnerships while improving diversity and inclusion in NIH's research response to COVID-19.[15] With 21 community-based teams, CEAL continues to effectively deliver trustworthy information to the most vulnerable communities across the U.S.[16]

Improving Health for all Humankind

Over the past three years of the COVID-19 pandemic, NIH has continued to fully support biomedical, behavioral, and social science research toward lengthening life and reducing illness for all people. For example, NIH is driving research to find scientific solutions to address the nation's opioid crisis.[17] In 2021 alone, there were more than 100,000 overdose deaths in the U.S., the majority involving opioids.[18] To combat this crisis, the NIH Helping to End Addiction Long-term (HEAL) Initiative® is working to enhance pain management and to improve prevention and treatment strategies for opioid misuse and addiction.[19] As part of this initiative, in 2019 NIH launched the HEALing Communities Study in four states significantly impacted by the opioid epidemic, working to test comprehensive, evidence-based strategies that aim to reduce opioid-related deaths.[20] The task is even more urgent since the COVID-19 pandemic fueled a nearly 30 percent increase in overdose deaths in 2020, the highest 12-month increase in decades. Throughout 2021, the HEAL Initiative® funded $2 billion to more than 700 research projects that address opioid misuse and pain management.

Cancer research also remains a top priority for NIH, with a broad, comprehensive portfolio of research dedicated to cancer prevention, detection, and treatment. Due in part to NIH-funded research, cancer deaths continue to decline in the U.S. From 2015-2019, overall cancer death rates decreased by 2.1 percent per year, continuing a 20-year trend of declining mortality due to improvements in understanding the causes of and treatments for cancer.[21] NIH has continued to invest in research on immunotherapies in which a patient's own immune system is primed to attack malignant cancer cells.[22] While immunotherapy treatment on its own is moderately effective, NIH research has helped to explain why

[14] https://www.nhlbi.nih.gov/news/2020/COVID-19-nih-funds-community-engagement-research-efforts-areas-hardest-hit
[15] https://covid19community.nih.gov/about
[16] https://covid19community.nih.gov/community-engagement-teams
[17] https://heal.nih.gov/news/heal-research-opioid-public-health-crisis
[18] https://heal.nih.gov/files/2022-10/heal-about-fact-sheet.pdf
[19] https://heal.nih.gov/about
[20] https://directorsblog.nih.gov/2019/05/14/study-finds-easier-access-to-naloxone-cuts-opioid-deaths/
[21] https://www.cancer.gov/news-events/press-releases/2022/annual-report-to-the-nation-2022
[22] https://directorsblog.nih.gov/2020/01/30/working-to-improve-immunotherapy-for-lung-cancer/

this treatment is successful only some of the time, leading to new research on combination therapies for better outcomes. NIH-funded research on precision cancer medicine found that individualized cancer treatments involving combination therapies, including new therapies that target a cancer's specific genes and molecules, led to better outcomes and longer life.[23]

NIH has been pushing scientific boundaries with novel and innovative technologies that open new avenues of biomedical research that were previously impossible. This is clearly evident as NIH-supported researchers harness artificial intelligence (AI) to efficiently process huge datasets of biological and health information and detect patterns that indicate health status or outcomes.[24] For example, AI has been used to diagnose brain tumors in real time, allowing brain surgeons to make immediate life-saving treatment decisions within the surgical suite.[25] The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative is revolutionizing our understanding of the human brain, and through its investment in new technologies has contributed to the development of a new dynamic picture of the brain that, for the first time, more accurately and precisely shows how individual cells and complex neural circuits interact in both time and space.[26] Researchers can now see specific neurons and how they connect to each other within the nervous system.[27,28]

NIH's neuroscience research investment has also contributed to a greater understanding of neurological disorders, such as obsessive compulsive disorder, and techniques to treat them, such as deep brain stimulation.[29] In addition, through the tissue chip program,[30] NIH investments in physical models of tissues and organ systems to support clinical treatment development[31] have led researchers to make unprecedented strides toward curing diabetes by creating replicas of pancreatic tissue in the lab that have been shown to treat diabetes in mice, suggesting potential cures in humans.[32]

Through all of this, NIH has continued to be a responsible steward of the public tax dollars, living up to President Roosevelt's charge 80 years ago. NIH continues to invest in research to reduce health disparities,[33,34] and in 2021 launched the UNITE initiative with aims to identify and address structural racism within the NIH-supported and the greater scientific community.[35] NIH also continues to invest in training the next generation of researchers whose diversity reflects the diversity of the nation.[36] Over this

[23] https://directorsblog.nih.gov/2019/04/30/personalized-combination-therapies-yield-better-cancer-outcomes/
[24] https://directorsblog.nih.gov/2019/05/07/whole-genome-sequencing-and-ai-yields-same-day-genetic-diagnoses/
[25] https://directorsblog.nih.gov/2020/01/14/artificial-intelligence-speeds-brain-tumor-diagnosis/
[26] https://braininitiative.nih.gov/
[27] https://directorsblog.nih.gov/2021/08/10/the-amazing-brain-visualizing-data-to-understand-brain-networks/
[28] https://directorsblog.nih.gov/2021/08/03/the-amazing-brain-toward-a-wiring-diagram-of-connectivity/
[29] https://directorsblog.nih.gov/2021/08/05/the-amazing-brain-deep-brain-stimulation-for-ocd/
[30] https://ncats.nih.gov/tissuechip
[31] https://directorsblog.nih.gov/2019/09/26/body-on-a-chip-device-predicts-cancer-drug-responses/
[32] https://directorsblog.nih.gov/2020/09/24/insulin-producing-organoids-hope-for-treating-type-1-diabetes/
[33] https://www.nih.gov/news-events/news-releases/nih-invest-29-million-address-covid-19-disparities
[34] https://www.nimhd.nih.gov/about/strategic-plan/
[35] https://www.nih.gov/ending-structural-racism/unite
[36] https://extramural-diversity.nih.gov/building-participation/recruitment-retention

reporting period, NIH has hired many new leaders[37,38,39,40,41,42,43,44] who will continue to guide NIH's efforts and vision to improve the health and wellbeing of all over the next three years.

Although many health-related challenges still lie ahead, continuing investment in NIH research offers hope to patients, families, and caregivers solutions that are within reach. Within this report, you will find numerous examples of how NIH capitalizes on the many promising opportunities to improve human health while also supporting the needs of the biomedical research community, helping to successfully meet those challenges and achieve better health for all.

—Lawrence A. Tabak, D.D.S., Ph.D.

Acting Director of the National Institutes of Health

[37] https://directorsblog.nih.gov/2018/11/27/new-nccih-director/
[38] https://directorsblog.nih.gov/2019/01/07/new-nibib-director/
[39] https://directorsblog.nih.gov/2019/09/04/new-nidcd-director/
[40] https://directorsblog.nih.gov/2020/10/16/a-new-director-for-ninr/
[41] https://directorsblog.nih.gov/2020/10/15/welcome-to-new-nidcr-director/
[42] https://directorsblog.nih.gov/2020/11/17/new-director-for-nei/
[43] https://directorsblog.nih.gov/2021/02/16/swearing-in-new-niams-director/
[44] https://directorsblog.nih.gov/2020/01/27/new-chief-executive-officer-for-all-of-us/

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.[45]

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:

1. Research on the causes, diagnosis, prevention, and cure of human diseases
2. Research on the processes of human growth and development
3. Research on the biological effects of environmental contaminants
4. Research on the understanding of mental, addictive, and physical disorders
5. 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 OD and 27 ICs, NIH employs approximately 18,000[46] full-time equivalent employees and is the steward of an approximately $43 billion in discretionary authority received from direct appropriations and *21st Century Cures Act* allocation (as of FY 2021).[47] The leadership and financial support NIH provides to biomedical, behavioral, and social science researchers extends throughout our nation and the world.

[45] https://www.nih.gov/about-nih/what-we-do/mission-goals
[46] https://www.edi.nih.gov/people/resources/advancing-racial-equity/nih-workforce-profile-fy21q02#01
[47] https://officeofbudget.od.nih.gov/pdfs/FY22/Approp%20History%20by%20IC%20FY%202020%20-%20FY%202022.pdf

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

Institutes and Centers

The 27 NIH ICs are organized with a focus on and expertise in a specific disease (e.g., cancer, diabetes), an organ system (e.g., heart, eye), a life stage (e.g., pregnancy, childhood, aging adulthood), an overarching field of science (e.g., genomics, nursing, environmental health), or a technology (e.g., biomedical imaging, bioengineering, biomedical informatics, information technology (IT)). The priorities of each IC are guided by its mission[48] and strategic plan,[49] which are harmonized with NIH's overall mission[50] and the NIH-Wide Strategic Plan.[51] The ICs *support* research and research training through extramural activities, and most ICs also *conduct* research and research training through intramural activities.

Listing of ICs

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

- National Cancer Institute (NCI)
- National Center for Complementary and Integrative Health (NCCIH)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of General Medical Sciences (NIGMS)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

[48] https://www.nih.gov/institutes-nih/list-nih-institutes-centers-offices
[49] https://report.nih.gov/reports/strategic-plans
[50] https://www.nih.gov/about-nih/what-we-do/mission-goals
[51] https://www.nih.gov/about-nih/nih-wide-strategic-plan

- 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 many offices that provide expert advice to the NIH Director and their 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:

- Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
- Office of Equity, Diversity, and Inclusion (EDI)
- Office of the Chief Information Officer (OCIO)
- Office of Communications and Public Liaison (OCPL)
- Executive Office (ODEO)
- Office of Extramural Research (OER)
- Office of Federal Advisory Committee Policy (OFACP)
- The NIH Branch of the Health and Human Services (HHS) Office of the General Counsel's (OGC) Public Health Division
- Office of Intramural Research (OIR)
- Office of Legislative Policy and Analysis (OLPA)
- Office of Management (OM)
- Office of Ombudsman/Center for Cooperative Resolution (OOCCR)

- Office of Science Policy (OSP)
- NIH Ethics Office (NEO)
- Office of the Chief Officer for Scientific Workforce Diversity (SWD)

Division of Program Coordination, Planning, and Strategic Initiatives

The role of the DPCPSI[52] 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 Acquired Immunodeficiency Syndrome (AIDS) Research (OAR), the Office of Behavioral and Social Sciences Research (OBSSR), the Office of Disease Prevention (ODP), the Office of Dietary Supplements (ODS), the Office of Data Science Strategy (ODSS), the Office of Nutrition Research (ONR), the Office of Research Infrastructure Programs (ORIP), the Office of Research on Women's Health (ORWH), the Office of Strategic Coordination (OSC), which manages the NIH Common Fund, the Sexual and Gender Minority Research Office (SGMRO), and the Tribal Health Research Office (THRO). Many of these OD program offices fund research using IC award-making authorities. ICs often partner with one of these program offices to supplement their funding for a specific program or project. However, ORIP directly funds research.

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

NIH Common Fund programs are intended to be:

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

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

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

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

The mission of ODP is to improve public health by increasing the scope, quality, dissemination, and impact of prevention research supported by NIH. In addition, the Tobacco Regulatory Science Program (TRSP), a component of the ODP, coordinates the trans-NIH collaborative effort with the FDA's Center for Tobacco Products to conduct tobacco and nicotine research to inform the FDA's tobacco regulatory priorities, including e-cigarettes. With the passage of the *2009 Family Smoking Prevention and Tobacco Control Act* (*Tobacco Control Act*), the FDA acquired the authority to regulate the manufacture, marketing, and distribution of tobacco products to protect public health. Within the framework of the Tobacco Control Act, the NIH and FDA formed this partnership to foster tobacco regulatory research. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

ODSS catalyzes new capabilities in biomedical data science by providing NIH-wide leadership and coordination for modernization of the NIH data resource ecosystem, development of a diverse and talented data science workforce, and building strategic partnerships to develop and disseminate advanced technologies and methods.

In 2021, the newest DPCPSI office, ONR, was transferred from NIDDK to DPCPSI to enhance engagement of the NIH ICs in implementing the 2020-2030 Strategic Plan for NIH Nutrition Research, to develop new collaborations and relationships focused on nutrition research within and outside NIH, and to ensure coordination of and leadership for nutrition research across the agency.[53]

ORIP contributes to the NIH mission by working to support innovative research aimed at protecting human health, training scientists and developing scientific infrastructure, and promoting integrity, public accountability, and societal responsibility in scientific research.

Established in 1990, ORWH[54] is the first PHS office dedicated specifically to promoting research on the health of women within and beyond the NIH scientific community. ORWH publishes the *Report of the*

[53] https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-establishment-office-nutrition-research-within-nih-office-director
[54] https://orwh.od.nih.gov/

Advisory Committee on Research on Women's Health; as required by Section 486(d)(5)(B) and 486B(b) of the *PHS Act*. This report is included in Appendix B.

THRO[55] and SGMRO[56] were established in 2015 to coordinate NIH activities relating to tribal health and sexual and gender minorities, respectively. More information on the activities of these offices is included in the Minority Health and Health Disparities section of Chapter 3.

DPCPSI also plans, supports, and provides technical assistance in the development of program evaluations and manages planning and reporting activities that support the U.S. Department of HHS' implementation of the *Government Performance and Results Act (GPRA)* and the *GPRA Modernization Act*, as well as other government-wide performance assessment activities (see Training and Career Development Programs Section in this chapter) and portfolio analysis activities.

Office of Extramural Research

OER[57] is the OD office that provides the corporate framework for NIH administration of research grants, ensuring scientific integrity, public accountability, and effective stewardship of the NIH extramural research portfolio. Offices within OER include the Office of Policy for Extramural Research Administration, the Office of Research Reporting and Analysis, the Office of Laboratory Animal Welfare, the Strategic Management and Contracts Office, the Office of Electronic Research Administration, the Division of Communications and Outreach, the Office of Small Business Education and Entrepreneurial Development, the Division of Biomedical Research Workforce, and the Division of Human Subjects Research.[58]

Office of Intramural Research

OIR[59] 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 Animal Care and Use, the Office of Intramural Training and Education, the Office of Human Subjects Research Protections, the Office of NIH History and Stetten Museum, and the Office of Technology Transfer.[60] In addition, OIR runs four NIH-wide early-career faculty recruitment and career development programs, each aimed at a different segment of the intramural research workforce and serves a different strategic aim of the NIH Intramural Research Program (for more information, please see section on Focusing on NIH's Workforce below). OIR formulates and disseminates intramural research policy and leads and administers the NIH-wide Central Tenure Committee.[61]

Collaboration Between Institutes, Centers, and Offices

Although NIH comprises a myriad of Institutes, Centers, and Offices (ICOs), all working toward achieving their mission, they do not operate in silos but rather interact in a highly collaborative fashion. Today, more

[55] https://dpcpsi.nih.gov/thro
[56] https://dpcpsi.nih.gov/sgmro
[57] https://grants.nih.gov/grants/oer.htm
[58] https://grants.nih.gov/aboutoer/welcome.htm
[59] https://oir.nih.gov/about
[60] https://oir.nih.gov/about/offices
[61] https://oir.nih.gov/sourcebook/committees-advisory-ddir/central-tenure-committee-ctc

than ever, NIH ICOs work together in new ways to leverage their unique strengths and resources. These collaborations can be formal or informal and may involve sharing financial resources, materials, or specimens. Often, collaboration takes the form of sharing scientific expertise. By maximizing resources, these NIH-wide initiatives serve to advance medical research in all disease areas and across the basic, translational, and clinical research continuum.

ICO Research Collaboration Reporting

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

Extramural and Intramural Research Programs

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

Extramural Research Program

More than 80 percent of NIH funding is awarded to the extramural biomedical and behavioral research community. The extramural research community is composed of scientists, clinicians, and other research personnel affiliated with nearly 2,700 organizations,[62] including universities, medical schools, hospitals, small businesses, and other research facilities located in all 50 states, the District of Columbia, Puerto Rico, Guam, the U.S. Virgin Islands, and other countries. In FY 2021, NIH funded the research of more than 35,000 principal investigators through research project grants,[63] which supported many thousands of additional personnel. With NIH support, these investigators and their research teams conduct the vast majority of research NIH supports to achieve its mission.

The NIH Deputy Director for Extramural Research provides leadership and coordinates policy, guidance, and oversight for ICO 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.

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

[62] https://nexus.od.nih.gov/all/2022/03/07/fy-2021-by-the-numbers-extramural-grant-investments-in-research/
[63] https://nexus.od.nih.gov/all/2022/05/03/how-many-researchers-the-fy-2021-cumulative-investigator-rate/

closeout of awards. eRA also provides services to other operating divisions of HHS and other federal agencies.

Grants Overview

The *NIH Guide for Grants and Contracts*[64] is the official publication for NIH funding opportunities. NIH advertises availability of grant and cooperative agreement support through funding opportunity announcements (FOAs), and also announces Requests for Proposals for R&D contract solicitations.[65] In addition to the *NIH Guide for Grants and Contracts*, applicants can also find FOAs on *Grants.gov*.

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

NIH uses activity codes which are specific grant types to differentiate the wide variety of research-related programs the agency supports. For example, the R01 grant type 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 include the following:

- R41/R42 and R43/R44 awards for the Small Business Technology Transfer (STTR) program and the Small Business Innovation Research (SBIR) program, respectively
- R21 awards for exploratory/developmental research projects
- R15 Academic Research Enhancement Awards to support small-scale research projects at educational institutions that have not been major recipients of NIH research grant funds
- F32 postdoctoral individual fellowship awards under the National Research Service Award (NRSA)
- T32 awards for enabling institutions to recruit individuals selected by the program leadership for predoctoral and/or postdoctoral research training in specified scientific areas
- K01 career development awards to provide support and protected time to individuals with a Ph.D. or D.V.M. for intensive, supervised research career development experiences
- K08 and K23 career development awards to provide support and protected time to individuals with a clinical doctoral degree for intensive, supervised research career development experiences
- P01 awards for research program projects that are broadly based, multidisciplinary, often long-term research, and have a specific major objective or a basic theme
- P30 awards for shared resources and facilities at research centers

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

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

- U01 awards for discrete, specified, circumscribed projects to be performed by investigator(s) in an area representing their specific interests and competencies

Contracts Overview

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

NIH Peer-Review Process

The core values of peer review[66] drive the NIH to seek the highest level of ethical standards, and form the foundation for the laws, regulations, and policies that govern the NIH peer review process. The NIH dual peer review system is mandated by statute in accordance with section 492 of the *Public Health Service Act* and federal regulations governing scientific peer review of research grant applications and research and development contract projects.[67] NIH policy is intended to promote a process whereby grant applications submitted to the NIH are evaluated on the basis of a process that strives to be fair, equitable, timely, and free of bias. The 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.

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

To ensure that NIH grant applications receive fair, independent, expert, and timely scientific reviews, free from inappropriate influences, CSR developed bias awareness and mitigation training for reviewers

[66] https://grants.nih.gov/grants/peerreview22713webv2.pdf
[67] https://www.govinfo.gov/app/details/CFR-2007-title42-vol1

specifically targeted toward mitigating the most common biases in the peer review process.[68] The training includes personal testimonials, interactive exercises, and a narrated mock study section demonstrating techniques to intervene – all based on real-life examples. The training launched in August 2021.[69] Recent feedback suggests that the training was well received and effective.[70]

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

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

Funding Decisions

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

Some of the ICs publish paylines as part of their funding strategies to guide applicants on their likelihood of receiving funding. Application scores can be compared only against the payline for the FY when the application will be considered for funding, which is not necessarily the year when it was submitted. Advisory Councils consider, evaluate, and make recommendations on applications that score both within and outside the payline.[71]

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

[68] https://public.csr.nih.gov/AboutCSR/Evaluations#reviewer_demographics
[69] https://public.csr.nih.gov/AboutCSR/Address-Bias-in-Peer-Review
[70] https://public.csr.nih.gov/sites/default/files/2022-04/Reviewer_Bias_Training_Survey_Report_2022-01_Council_Round_final.pdf
[71] 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.

justification, to support highly innovative or high-program-priority applications that score beyond the payline or outside the funding limit.

Before issuing an award, NIH ensures that the planned research meets all requirements for safe and responsible conduct. This includes making sure that the research has undergone all necessary reviews and has obtained required approvals from boards and committees charged with protection of human subjects; inclusion of minorities, women, and individuals across the lifespan; 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 grant recipients. 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.[72] NIH also monitors compliance with federal laws and policies pertaining to protection of human subjects, the care and use of vertebrate animals used in research, data sharing, the NIH Public Access Policy, and other matters. In addition, oversight of clinical research may involve data and safety monitoring and monitoring of inclusion of clinical research participants by sex, gender, race, and ethnicity.

Other Transactions

An Other Transactions Authority (OTA) allows for Federal Government agencies to enter into Other Transactions (OTs), which is a unique type of legal instrument other than a contract, grant, or cooperative agreement.[73] Generally, this awarding instrument is not subject to the FAR, nor grant regulations unless otherwise noted for certain provisions in the terms and conditions of award. It is, however, subject to the OT authority that governs the initiative as well as applicable legislative mandates. Through unconventional processes, OTs allow NIH to address rapidly evolving research areas, especially those that are multi-disciplinary or relate to urgent public health situations when the future direction of the science is constantly changing and unknown. NIH staff can also help bring experts together in novel ways through OT awards, such as through engaging non-traditional partners, companies, advocates, and individuals. Similar to NIH's role with contracts and cooperative agreements, NIH can take a more active and substantive collaborative role in scientific design and program management beyond traditional grant administrative and oversight functions.

[72] https://grants.nih.gov/grants/policy/nihgps/HTML5/section_8/8.4_monitoring.htm
[73] https://nexus.od.nih.gov/all/2022/03/23/its-not-a-grantits-not-a-contractits-an-other-transaction

Challenges and Prize Competitions

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

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

Intramural Research Program

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

The IRP seeks to be a dynamic research environment for new generations of imaginative scientists to conduct fundamental research that reveals new principles of biology and behavior, provides new understandings of human disease, and changes treatment and prevention paradigms. The IRP research environment is also designed to attract and train a highly talented and diverse cadre of scientists who will lead biomedical research in the 21st century. Its unique funding environment means the IRP can facilitate opportunities to conduct both long-term and high-impact science that would otherwise be difficult to undertake. The IRP has nurtured many Nobel Prize winners—winners of 25 prizes and counting—who either did the bulk of their award-winning research in the IRP or trained or worked in one of the IRP laboratories.[74]

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

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

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[75] 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 or tenure-track scientist and makes recommendations regarding continuation or modification of projects and adjustment of resources (e.g., budget, space, and personnel). Moreover, IC Scientific Directors are evaluated by an external committee every five years, and each IC intramural research program is reviewed, in its entirety, by a blue ribbon panel approximately every ten 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.

IRP accomplishments have been many and include profound advances in cancer treatment through immunotherapy, successful gene therapy treatment for sickle cell disease, and inventions in the fields of magnetic resonance imaging (MRI) and bioimaging. During FY 2019 to 2021, IRP scientist Harvey Alter won the Nobel Prize for his work on hepatitis C, Richard Youle won the Breakthrough Prize in Life Sciences for his groundbreaking research on Parkinson's disease, and Barney Graham won the Albert B. Sabin Gold Medal for his critical role in accelerating the development of multiple COVID-19 vaccines.

Several offices manage research training for the IRP. The Office of Intramural Training and Education (OITE) within the OIR 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 the scientific and professional skills needed to become independent researchers and leaders in the biomedical research community. The Office of Clinical Research Training and Medical Education in the NIH Clinical Center covers all aspects of clinical training. In addition, most of the individual ICs have a Training Director who oversees their trainees. These offices have established the IRP as the premier destination for biomedical research training, offering research opportunities in a richly diverse environment coupled with strong mentorship and work–life balance accommodation. This environment helped both trainees and junior faculty maintain their career trajectory during the COVID-19 pandemic and enabled and empowered the ICs to recruit, retain, and fuel for the future an increasingly diverse workforce.

The OIR also enables and administers the recruitment and mentoring of faculty into four career development programs. The Stadtman Tenure-track Scholars Program is aimed at early-career scientists who perform basic biomedical research. The Lasker Clinical Scholars Program is aimed at early-career

[75] 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.

physician-scientists who perform clinical research. The Distinguished Scholars Program enrolls faculty scientists already at NIH who have tangibly demonstrated dedication to engaging and empowering a diverse biomedical research workforce. Finally, the Independent Research Scholars Program enables extraordinarily talented and motivated postdoctoral fellows to begin their independent research careers earlier than usual. These programs serve to launch the research-intensive careers of outstanding scientists and physicians who go on to senior positions at NIH, academic institutions around the U.S., and industry.[76] The OIR also runs the Central Tenure Committee of NIH, which advises the NIH Deputy Director for Intramural Research on the readiness of faculty members to be awarded tenure.[77]

The OIR is responsible for trans-NIH oversight and coordination of the IRP, human subject protections, animal welfare, research integrity and reproducibility, training, policy development, laboratory safety, and technology transfer conducted within NIH laboratories and clinics. OIR coordination has resulted in obtaining full accreditation for a revised Institutional Review Board (IRB) system as well as accreditation from both the Association for the Accreditation of Human Research Protection Programs and Association for Assessment and Accreditation of Laboratory Animal Care International, a nonprofit organization that promotes the humane treatment of animals in science. Similarly, the OIR helped to enable a robust response to the COVID-19 pandemic that included the rapid creation and testing of a vaccine candidate, distribution of funding for COVID-related research, and the broad sharing of knowledge through a comprehensive resource dashboard, listserv, and scientific lecture series.

The OIR is led by the NIH Deputy Director for Intramural Research, and the IRP within each IC is led by a Scientific Director who helps conduct oversight. A summary of policies governing intramural research can be found in the Intramural Research Program Sourcebook.[78]

Historical information about NIH—including the establishment of the categorical ICOs—is maintained by the NIH Office of History, a component of OIR that preserves records of significant NIH achievements, innovative exhibits, and educational programs to enhance understanding of NIH biomedical and behavioral research.[79]

NIH CC

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

---

[76] https://www.nih.gov/research-training/lasker-clinical-research-scholars; https://irp.nih.gov/careers/trans-nih-scientific-recruitments/stadtman-tenure-track-investigators; https://diversity.nih.gov/programs-partnerships/dsp; https://oir.nih.gov/sourcebook/personnel/ipds-appointment-mechanisms/research-fellow/independent-research-scholar-program

[77] https://oir.nih.gov/sourcebook/committees-advisory-ddir/central-tenure-committee-ctc

[78] https://oir.nih.gov/sourcebook.

[79] https://history.nih.gov/research/sources_legislative_chronology.html

The NIH CC opened its doors in 1953, and the scope of NIH research expanded significantly with the opening of the Mark O. Hatfield Clinical Research Center in 2005, which houses 200 patient beds and 93-day-hospital stations. In 2021, the CC admitted 3,120 patients, accounting for 31,728 inpatient days. Additionally, 62,499 outpatient visits occurred in 2020. This is about 50 percent lower than typical patient load, but this decrease was due to the ongoing COVID-19 pandemic. In addition to approximately 1,300 credentialed physicians, dentists, and postdoctoral researchers, the CC houses more than 830 nurses and 730 other allied health professionals, including pharmacists, dietitians, medical and imaging technologists, therapists, and medical records and supply staff. Since the hospital opened, it has hosted more than 530,000 clinical research participants. Because the CC is a research facility, only patients with specific and relevant kinds or stages of illness under investigation are admitted for treatment. The CC has no emergency room, and no labor and delivery services. Most patients are referred by their physicians, but approximately one-third self-refer via the Internet.

Figure 2. Aerial view of the Mark O. Hatfield Clinical Research Center (Building 10), NIH Campus, Bethesda, MD. Credit: NIH

Although the CC sponsors a small number of internal research programs conducted by its own staff, its primary role is to provide the necessary infrastructure for the intramural clinical research conducted by the ICs within the hospital. This infrastructure includes the staff, facilities, systems, and resources needed for safe and high-quality patient care in support of clinical research studies.

Known as the *House of Hope* to patients, the CC has played a vital role in a long list of medical milestones, including development of chemotherapy for cancer, the first use of an immunotoxin to treat a malignancy, identification of the genes that cause kidney cancer, leading to the development of six new, targeted treatments for advanced kidney cancer, the demonstration that lithium helps depression, the first gene therapy, the first treatment of AIDS (with azidothymidine), and the development of tests to detect the

human immunodeficiency and hepatitis viruses in blood, which led to a safer blood supply to use in clinically required blood transfusions.[80]

In the last few years, the CC has introduced significant changes to its governance (separating the oversight of clinical research science from the CEO's oversight of operational and hospital administrative management), established a new CC Mission and strategic aims, revised the Guiding Principles, and integrated a new CC Research Hospital Board (CCRHB). These changes have been grounded in an unwavering commitment by the CC workforce to fortifying a culture and practice of safety and quality.
The CC continues to build on its proud history of tackling the world's toughest public health challenges. For example, the CC has emerged at the forefront of addressing the Zika[81] and Ebola[82] crises. The CC's isolation facility, known as the Special Clinical Studies Unit, enables state-of-the-art care for patients with unusual or novel infectious diseases to participate in research protocols to mitigate any outbreaks. Like many hospitals, the CC has implemented new protocols and safety procedures in order to address the ongoing COVID-19 pandemic. Since the beginning of the pandemic, the CC has had an extremely low rate of transmission and has been involved in creating and managing an array of research protocols related to COVID-19.
In addition to the CC on the main campus, NIH supports satellite clinical research facilities through various ICs. For example, the NIEHS Clinical Research Unit, located on the Institute's North Carolina campus, is focused on studying the interactions of genetics and environmental exposures in the development of disease. It conducts pharmacokinetic studies on environmental chemicals and studies identifying populations at increased risk for exposure to these chemicals, with the goal of developing novel preventive and therapeutic strategies to address human disease.

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

[80] https://cc.nih.gov/welcome.html
[81] https://www.niaid.nih.gov/diseases-conditions/zika-vaccines
[82] https://cc.nih.gov/ebola1.html

Fostering a Talented Workforce

Vital to accomplishing NIH's mission to advance biomedical science and improve the health of the American people are the scientists who conduct the research and the administrators who support them. In supporting the biomedical research enterprise, NIH must not only fund the research, but also ensure that there is a robust, well-trained workforce of innovative, diverse, and dedicated researchers.[83] Furthermore, to effect real improvements in the health, NIH itself must be staffed by a talented, diverse, effective, and well-supported workforce. In 2019-2021, NIH invested in new and innovative ways to strengthen its workforce and the research community that it supports.

Supporting the Biomedical Workforce

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

Catalog of Research Training Activities

In response to the mandate under Section 403 (a)(4)(C)(iv) of the *PHS Act* to provide a catalog of research training activities, Appendix E includes a number of Ph.D. recipients by field of study who have been trained under the following:

- Ruth L. Kirschstein NRSA and NLM Research Training Grants, FY 2018, 2019, and 2020[84]
- Ruth L. Kirschstein NRSA *Individual* Fellowship Awards, FY 2018, 2019, and 2020

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

An ongoing challenge is the need to balance supporting the future of the biomedical research workforce with sustaining existing research programs. NIH has long understood that supporting the future biomedical workforce is essential to cutting-edge scientific advances and lasting impact on human health needs. Over the past decade, many groups have published data on the aging of the workforce and on the age distribution of NIH-funded researchers. A number of academic leaders have described and expressed concerns about the age at which scientists are first supported on an R01 award ("age at first R01"). Since the late 1990s, the percentage of NIH-funded investigators over the age of 60 has risen significantly

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

[84] FY 2021 data were not available at the time this report was prepared and will be included in the next Triennial Report.

compared with other age groups.[85] As noted on this NIH Open Mike blog, while age has been continuously increasing, the rate of increase has slowed over the last ten years.[86]

NIH has heard these concerns too and recognizes the potential impact on the future biomedical workforce. That is one of the reasons why, in the late 2000s, NIH implemented an Early-Stage Investigator policy and, after considering recommendations from the Advisory Committee to the Director (ACD),[87] the National Academies of Sciences,[88] and the *21st Century Cures* Act passed by Congress, NIH has, over the past few years, implemented its Next Generation Researchers' Initiative (NGRI). The NIH NGRI is continuing to address longstanding challenges faced by researchers trying to embark on and sustain independent research careers, as well as to promote the stability and diversity of the biomedical research workforce. Since the launch of this initiative, there has been steady growth in the number of early-stage investigators (ESIs) supported by NIH, increasing from 978 in FY 2016 (before NGRI started) to 1,513 in FY 2021.[89] During this time, the funding rate has also steadily increased for ESIs from 23.6 percent in FY 2016 to 28.0 percent in FY 2021.[90] Moving forward, NIH remains strongly committed to the goals of NGRI to fund more early-career investigators, retain meritorious at-risk scientists, and enhance the diversity of the biomedical research workforce.

Every IC and many OD offices support training programs specific to their mission. For example, the NIGMS R35 Maximizing Investigators' Research Award (MIRA) seeks to transform how fundamental biomedical research is supported by providing investigators with a heightened level of both scientific stability and flexibility, allowing investigators to follow new research directions and insights in real-time while simultaneously providing an extra year of financial support as part of a more coordinated scientific program (versus project) focus. MIRA also promotes early-stage investigator (ESI) inclusion in scientific research. The peer review process for MIRA applicants considers ESIs independently from well-established investigators, thus allowing each group of applicants to be examined relative to their peers.[91] As of FY 2019, MIRA has funded 455 ESIs and 533 Established Investigators. Through MIRA, scientists have been able to open new lines of research, including, for example, areas associated with chromosomal rearrangement and induced pluripotent stem cells. In addition, MIRA has directly contributed to an 83 percent increase in the number of ESIs supported by NIGMS.

Another NIGMS major program is the Institutional Development Award (IDeA), which builds research capacities at academic institutions located in states that have historically received a lower aggregate level of NIH funding.[92] By building organizational and workforce-related capacities in these states, the program

[85] NIH Advisory Committee to the Director (ACD) Next Generation Researchers Initiative Working Group. 2018. https://acd.od.nih.gov/documents/presentations/12132018NextGen_report.pdf.
[86] https://nexus.od.nih.gov/all/2021/11/18/long-term-trends-in-the-age-of-principal-investigators-supported-for-the-first-time-on-nih-r01-awards/
[87] https://www.acd.od.nih.gov/documents/presentations/12132018NextGen_report.pdf
[88] https://nap.nationalacademies.org/catalog/25008/the-next-generation-of-biomedical-and-behavioral-sciences-researchers-breaking
[89] https://nexus.od.nih.gov/all/2022/07/18/more-early-stage-investigators-supported-in-fy-2021/
[90] https://nexus.od.nih.gov/all/2021/07/12/data-on-implementing-nihs-next-generation-researchers-initiative/
[91] https://loop.nigms.nih.gov/2022/02/mira-renewals-award-rates-and-budget-changes/
[92] https://nigms.nih.gov/Research/DRCB/IDeA/Pages/default.aspx

enhances the ability of investigators to compete successfully for additional research funding while also addressing the specific needs of medically underserved communities. In addition to well-established and widely known components of the IDeA program, such as the Centers of Biomedical Research Excellence (COBRE), the IDeA Clinical and Translational Research (CTR) Network, and the IDeA-State Networks of Biomedical Research Excellence (INBRE), during FY 2019-2021, NIGMS also funded Regional Technology Transfer Accelerator Hubs for IDeA states in each of the four IDeA regions (central, northeast, southeast, and western regions of the U.S.). The goal of the accelerators is to provide consulting and skills development in entrepreneurship, technology transfer, management, small business finance, and other areas needed to transform important discoveries made in the lab into commercial products that address human health.

NHGRI created the Genomic Innovator Awards in 2018 to support early-career investigators who have made significant contributions to consortia and other team science efforts.[93] The awards provide crucial funds to support their independent research careers. NHGRI announced the six inaugural Genomic Innovator Awards in 2019, supported twelve more early career investigators in 2020, and an additional eleven awardees in 2021 - including researchers who are studying Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technologies, brain-related disorders, single-cell genomics, precision medicine, and how the field handles massive amounts of genomic data.

In FY 2019 and 2020, NIAMS maintained its Research Innovation for Scientific Knowledge program that encourages investigators to pursue unusual observations, test imaginative hypotheses, explore creative concepts, and discover ground-breaking paradigms within the NIAMS mission.[94] Successful applicants receive two or three years of support to test their bold ideas that challenge prevailing theories or practices. The program was paused in FY 2021 to allow staff to evaluate the outcomes with the potential to refine the opportunity.

The NIAMS Supplements to Advance Research (STAR) award program supports NIAMS investigators who recently renewed their first major independent award as they work to expand their research from a single, structured project into a broader, multi-faceted research program.[95] Reflecting NIAMS' commitment to early-career investigators, the STAR program aligns with the trans-NIH Next Generation Researchers Initiative.

[93] https://www.genome.gov/research-funding/Funding-Opportunities/Genomic-Innovator-Awards
[94] https://www.niams.nih.gov/grants-funding/funding-opportunities/research-innovations-scientific-knowledge-risk
[95] https://www.niams.nih.gov/grants-funding/funded-research/supplements-advance-research-star

Figure 4. Research training: students load proteins onto a gel that will separate them by size. Credit: Office of Intramural Training & Education, NIH

Through the NIEHS Research Intensive Short Courses and Educational Opportunities (NIEHS RISE), the Institute funds short-term research education activities with the goal of improving individual knowledge and skills needed to conduct environmental health research. The emphasis is on providing relevant hands-on and practical educational experiences related to the conduct of environmental health research. The first of these courses include: Environmental Health Research Institute for Nurse and Clinician Scientists, Endocrine-Disrupting Chemicals: Hazards and Opportunities, and Frontiers in Environmental Science and Health.

Since 1987, the NIEHS Worker Training Program has supported a national network of institutions that deliver high-quality, peer-reviewed safety and health curricula to hazardous waste workers and emergency responders in every region of the U.S.[96]

NINDS's Research Program Award is one of the Institute's signature programs. It provides a unique opportunity of up to eight years of grant funding versus the standard two- to five-year NIH grant.[97] The goal of this program is to help investigators make meaningful contributions to neuroscience by providing greater funding stability, flexibility, and support for their overall research project and freeing time from grant writing to better mentor their trainees.

NLM's university-based research training program supports biomedical informatics and data science research training programs in universities across the country.[98] The program focuses on original basic or applied research with one or more of the key biomedical application domains: health care or clinical

[96] https://www.niehs.nih.gov/careers/assets/docs/wtp_doe_accomplishments_20192020_508.pdf
[97] https://www.ninds.nih.gov/funding/about-funding/ninds-research-program-award-r35
[98] https://www.nlm.nih.gov/ep/GrantTrainInstitute.html

informatics, translational bioinformatics, clinical research informatics, public health informatics, and consumer health informatics.

In addition to supporting training programs and mentored research experiences, NIH offers short-term learning opportunities for scientists, regardless of career stage, to broaden and enrich their knowledge base and skillset. The Data and Technology Advancement (DATA) National Service Scholar Program, for example, brings experienced data and computer scientists and engineers to NIH to tackle challenging data science problems in biomedicine. The program encourages transformative approaches that lead to increased efficiency, innovative research, tool development, and analytics. To date, 13 DATA scholars have been recruited to two cohorts and placed in 11 ICOs for one-to-two-year positions, working on high-impact data and technology projects that aim to advance the landscape of biomedical data science.[99]

There is tremendous need for people to discover, develop, and disseminate the next generation of science and technology to improve human health through translational science. Education of translational scientists is critical to this need. To advance its educational mission, NCATS has released a new NCATS educational video, geared toward current and potential trainees, about translational science.[100, 101]

The NCATS Office of Strategic Alliances has developed a new translational science training program entitled Advancing Innovation through Mentorship (AIM). The AIM training program is based off the National Science Foundation's (NSF) Innovation Corps (or I-Corps) program, which uses experiential education to help researchers gain valuable insights into entrepreneurship, industry requirements, and challenges to translating their innovations into the marketplace. The NCATS AIM program helps explore technology ecosystems and how to identify opportunities for doing impactful research, as well as learning how to use "customer discovery" to identify what is the best market fit for a technology. The pilot cohort established in 2020 was conducted in collaboration with the NCI SBIR Center and NCI Technology Transfer Center.

To advance its translational science education mission, NCATS has partnered with Translation Together, a global collaboration of translational science organizations working to advance the science and understanding of biomedical translation, on the publication of a consensus paper on the fundamental characteristics of a translational scientist. The seven traits of a translational scientist that were identified are boundary crosser, team player, process innovator, domain expert, rigorous researcher, skilled communicator, and systems thinker.[102] The paper provides a framework for the field's culture and values.[103]

In FY 2020, OBSSR, NCI, NHLBI, NIA, NIAAA, NICHD, NIDDK, NIDA, NIMH, NINR, and NIMHD, awarded eight grants to create the Training in Advanced Data Analytics for Behavioral and Social Sciences Research

[99] https://datascience.nih.gov/meet-the-2021-data-scholars
[100] https://ncats.nih.gov/training-education/skills
[101] https://www.youtube.com/watch?v=TnHLo-hCssg
[102] https://ncats.nih.gov/training-education/skills
[103] Gilliand CT, et al. *ACS Pharmacol Transl Sci.* 2019 May 2;2(3):213-216. PMID: 32259057.

program.[104] This new five-year training program will incorporate computational and data science analytic approaches directly into behavioral and social sciences predoctoral degree programs to support the development of a cohort of specialized scholars pursuing careers in health-related research with competencies in data science analytics.[105] This funding opportunity was designed to address key methodology innovation and training priorities, and will offer virtual lecture series that cover advanced data analytics and data science underlying modern behavioral and social sciences research, with presentations from experts showing the basics of data management, representation, computation, statistical inference, data modeling, causal inference, and various other topics relevant to *big data* and teaching for behavioral and social sciences researchers.[106]

OBSSR and participating ICOs also re-issued Short Courses on Innovative Methodologies and Approaches in the Behavioral and Social Sciences,[107] which support educational activities that complement and/or enhance the training of a workforce to meet the nation's biomedical, behavioral, and clinical research needs.[108] This funding opportunity is designed to fill educational gaps and needs in the BSSR community that are not being addressed by existing educational opportunities.

The ODP Early-Stage Investigator Lecture award recognizes early-career prevention scientists who have not successfully competed for an R01 or R01 equivalent NIH research grant, but who have made significant contributions to their fields and are poised to become future leaders in prevention research.[109] Award priority is given to nominees conducting applied prevention research on any of the leading risk factors for or causes of death and disability in the United States. The ODP also considers nominations in the areas of reducing health disparities, advancing research on methods and measurement, or disease screening. The award winner is invited to give a lecture at the NIH. The awardee is also offered an opportunity for professional networking with NIH program directors and scientists.

ODP hosts the Methods: Mind the Gap webinar series focused on best practices for research design, measurement, intervention, data analysis, and other methods of interest in prevention science.[110] Participants ask questions at the end of the presentation and the recording, slides, key references, and names of experts in the area are posted on the ODP website after each webinar. Twenty-three webinars were held during FY 2019 – 2021. Topics included using data science in suicide prevention work, approaches to improving dietary assessment to better gauge the risk of chronic disease, and design and analytic methods for group-based interventions.

ORIP has a unique mission to train veterinary scientists to engage in biomedical research. Accordingly, ORIP training and career development programs for veterinary students and veterinarians are designed

[104] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-011.html
[105] https://obssr.od.nih.gov/news-and-events/news/obssr-t32-training-in-advanced-data-analytics-for-behavioral-and-social-sciences-research-grants-awarded
[106] https://www.youtube.com/playlist?list=PL0S7weWH90ngO1dvgHdZLf-qhUH1---j0
[107] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-012.html
[108] https://obssr.od.nih.gov/news-and-events/news/obssr-r25-short-courses-innovative-methodologies-and-approaches-behavioral-and
[109] https://prevention.nih.gov/news-events/early-stage-investigator-lecture
[110] https://prevention.nih.gov/education-training/methods-mind-gap

to (1) encourage talented veterinary scientists to pursue a career in biomedical research; (2) advance NIH-funded translational research by increasing the participation and collaboration of veterinary scientists trained in biomedical research; and (3) provide unique training programs designed specifically for veterinarians and veterinary students that are not duplicated by NIH ICs. Past awardees have focused on research topics such as HIV/AIDS, cancer, and translational science. For example, a past ORIP-supported recipient of a K01 Special Emphasis Research Career Award[111] oversees the One Health Laboratory at Johns Hopkins University to examine the interface of bacteria and hosts to reduce microbe-mediated disease in humans and animals.[112,113]

To stimulate the funding of new applications and to improve the current landscape of NIH-funded HIV early-stage/early-career investigators (ESI/ECI), OAR provided supplement funding to ICs to support meritorious ESI/ECI grant proposals related to HIV/AIDS research that did not meet the IC's payline. This one-year funding was used to fund the first year of an R01 grant or to support a R56 Bridge Award. In FY 2020, OAR provided funding to support nine HIV-related projects targeting ESI/ECI. In FY 2021, OAR provided funding to support seven HIV-related awards to ESI/ECI.

The NIH HEAL Initiative® supports several training, mentorship, and career development programs to build capacity for conducting the wide range of projects in the initiative's research portfolio. These include retraining existing talent to meet urgent national needs by funding early career scientists or clinicians working in addiction treatment to develop expertise in implementation science. The program will also expand the pain treatment workforce to provide novel pain management solutions in the future. For example, HEAL provides support for junior clinical pain researchers to receive mentorship to support their work towards independent clinical pain research careers. The HEAL Enhancing Career Development in Clinical Pain Research program leverages NIH's K24 award mechanism to provide support for researchers taking part in one of HEAL's clinical pain programs to implement mentoring plans to provide junior investigators with the tools and skills needed for an independent clinical pain research career.[114]

NHGRI's Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG) Scholars Program is an education collaborative that facilitates interactions among professional societies, agencies, and health systems.[115] It intends to enhance the accrual of knowledge and skill among practitioners applying genomic results to clinical care. The Scholars Program, launched in 2020, provides students with exposure to the broader genomics community and experts in the field, with the opportunity to work on a genetics/genomics-related education projects under the mentorship of an ISCC-PEG member.

Biomedical Workforce Diversity

The diversity of research training participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Of the FY 2021 trainees and fellows who reported their race and ethnicity, 62.7

[111] https://orip.nih.gov/about-orip/research-highlights/profile-veterinary-scientist-meghan-davis-dvm-phd-mph
[112] Dalton KR, et al. *Microorganisms.* 2021 May 13;9(5):1054. PMID: 34068292.
[113] Coffman VR, et al. *Am J Ind Med*. 2021 Aug;64(8):688-698. PMID: 34091939.
[114] https://heal.nih.gov/research/clinical-research/career-development-clinical-pain-research
[115] https://www.genome.gov/careers-training/Professional-Development-Programs/ISCC-PEG-Scholars-Program

percent were White, 16.0 percent were Asian, 8.3 percent were Black or African American, 14.2 percent were Hispanic or Latino, 0.8 percent were American Indian or Alaska Native, 0.2 percent were Native Hawaiian or Other Pacific Islander, and 5.5 percent reported more than one race. 57.4 percent of trainees and fellows in FY 2021 were women.

Across NIH, NRSA training grants and fellowships help promote research training opportunities for individuals from diverse backgrounds, including those from populations and backgrounds typically underrepresented in research. At the graduate and postdoctoral levels, NIH policy requires institutional training grant directors to take steps to recruit a diverse pool of candidates for training programs from underrepresented groups, including racial and ethnic minorities and individuals with disabilities. Through the Ruth L. Kirschstein NRSA for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research, NIH also provides graduate students from diverse backgrounds, including those from underrepresented groups, with opportunities to pursue research training through individual fellowship awards.[116] As recruiting talented individuals into research training programs requires a pool of prepared applicants from which to draw, NIH offers undergraduate research training to honors students at selected institutions who are interested in a research career and who intend to pursue postgraduate education leading to a Ph.D., M.D./Ph.D., or other combined research degree. The Chief Officer for Scientific Workforce Diversity (COSWD) Office convened in June 2019 distinguished senior thought leaders who have established and led national efforts to enhance workforce diversity and inclusion in the NIH-funded biomedical research workforce.[117] This gathering, the inaugural Advancing Diversity Programs Conference, also invited early-career scientists to share their unique perspectives and first-hand knowledge on successful strategies and programs with demonstrated success for enhancing diversity and inclusion.

Diversity Catalysts form an 83-person committee of nominated representatives from NIH ICOs that was formed in 2014 by the NIH Director and COSWD. The Diversity Catalysts provide rapid and effective input to the COSWD Office at early stages of diversity, equity, inclusion, and accessibility (DEIA) strategy development, implement and evaluate evidence-based DEIA strategies through pilot and expanded initiatives, within or across ICs, share effective DEIA initiatives, lessons learned, and related insights with ICs to diffuse best practices across NIH, and advise ICs on strategies for tailoring DEIA initiatives to specific IC cultures.[118] The Catalysts meet once or twice per quarter and have helped to adopt and disseminate the following tools from the SWD Toolkit within their ICs: (1) COSWD Recruitment Search Protocol – to identify qualified scientific researchers from diverse backgrounds; (2) Implicit Bias Education Modules – to create awareness of implicit bias and reduce its impact; and (3) Prototype Career-Development Conference - for early-career scientists from diverse backgrounds. They are currently being called upon to highlight the top diversity initiatives at each IC, noting outcomes, costs, generalizable principles, and opportunities for joint programming.

[116] https://researchtraining.nih.gov/programs/fellowships/f31#
[117] https://diversity.nih.gov/sustaining-diversity/ADPC
[118] https://diversity.nih.gov/sustaining-diversity/diversity-catalysts

The Scientific Workforce Diversity Seminar Series (SWDSS) was initiated in 2021.[119] It hosts renowned researchers who have contributed to the growing body of knowledge on pressing topics relevant to scientific workforce diversity, including, but not limited to, evidence-based interventions. The purpose of the series is to keep scientific workforce diversity issues at the forefront, to share the latest research on these topics, and to engage with professionals and researchers within and outside of the NIH.

The goal of the Fostering Cohort Recruitment (FCR) Virtual Forum was to galvanize the wider scientific community around the success of cohort recruitment models geared toward enhancing DEIA for faculty. The FCR Virtual Forum explored faculty cohort recruitment adoption and dissemination, its impact on DEIA, practices that make it successful, barriers that might exist, and ways to effectively evaluate both implementation and outcomes.[120] It introduced attendees to faculty cohort programs and delved into the science behind them. The FCR Virtual Forum was free and open to the public. It was intended for implementers and potential implementers of faculty cohort programs. A recording and other meeting materials were made available after the event.

The Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program is managed by NIH Common Fund with involvement from COSWD, NHLBI, NIMHD, NINDS, and NCI.[121] FIRST aims to enhance and maintain cultures of inclusive excellence in the biomedical research community. *Inclusive excellence* refers to cultures that establish and sustain scientific environments that cultivate and benefit from a full range of talent. NIH aims to facilitate institutions in their building a self-reinforcing community of scientists, through recruitment of a critical mass of early-career faculty who have a demonstrated commitment to inclusive excellence. The program also seeks to have a positive impact on faculty development, retention, progression, and eventual promotion, as well as develop inclusive environments that are sustainable. The concept for this program originated in the COSWD Office, and it is to replicate the IRP Distinguished Scholars Program that has been successful in increasing the diversity of tenure track scientists. The COSWD Office will continue programming to support the concept of cohort recruitment given the robust response to the initial FIRST solicitation. As of the end of FY 2021, two FOAs were issued.[122,123] As of September 2021, an initial selection of seven institutions received NIH funding. One institution—Morehouse School of Medicine—received funding for FIRST Coordination and Evaluation Center to promote inclusive excellence. Six other institutions received funding for faculty cohort development: Cornell University, Icahn School of Medicine at Mount Sinai, Drexel University, University of Alabama at Birmingham, Florida State University, and San Diego State University. Additional funding rounds are forthcoming.

The Scientific Workforce Diversity Toolkit[124] is a resource for NIH scientists and the broader community with information regarding how to increase diversity within institutions, information about implicit bias

[119] https://diversity.nih.gov/science-diversity/swd-seminar-series
[120] https://diversity.nih.gov/science-diversity/swd-seminar-series-february
[121] https://commonfund.nih.gov/first
[122] https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-20-022.html
[123] https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-21-025.html
[124] https://diversity.nih.gov/sites/coswd/files/images/SWD_Toolkit_Interactive-updated_508.pdf

and how to reduce it, and information and benefits of mentoring. This toolkit has served as a basis for the COSWD Office to provide evidence-based guidance to staff across NIH.

The ACD Working Group on Diversity (WGD) was formed in 2013 in response to the ACD Working Group on Diversity in the Biomedical Research Workforce (WGDBRW) recommendations. The ACD WGD is a permanent working group of the ACD charged with assisting the ACD to develop effective diversity-related strategies for NIH and includes two subgroups: the Diversity Program Consortium (DPC) subgroup, which gives advice to the NIH Director regarding DPC's initiatives, and the Individuals with Disabilities subgroup, formed in summer 2021 and comprised of 12 external experts, to prepare a report containing suggestions for how NIH might bolster its efforts to support individuals with disabilities in biomedical research.[125] If recommendations are endorsed by the ACD, COSWD will be tasked with determining how to implement them.

The Administrative Diversity Supplement to Promote Diversity in SBIR provides additional funding to small businesses holding an NIH Small Business Innovation Research or Small Business Technology Transfer award and aims to recruit and support students, postdoctoral students, and eligible investigators from diverse backgrounds, including those from groups that have been shown to be underrepresented in health-related research, women, and socially or economically disadvantaged individuals.[126] Through broad participation by all ICOs and three Centers for Disease Control and Prevention (CDC) centers, the administrative supplements have provided support for research and entrepreneurial experiences to 88 individuals throughout the continuum from undergraduate to the faculty level.

Women in the biomedical workforce face many institutional and systemic barriers that impede their career success and advancement. ORWH launched various initiatives to address challenges women face in the workforce. ORWH released the NOSI: Interventions Designed to Change the Culture to Mitigate or Eliminate Sexual Harassment in the Biomedical Research Enterprise[127] to inform potential applicants of the NIH's interest in supporting research on interventions designed to change the culture to mitigate or eliminate sexual harassment in the biomedical research enterprise. ORWH also issued a FOA to support the Advancing Gender Inclusive Excellence Coordinating Center (U54).[128] ORWH also issued three NOSIs to address the attrition of women from the workforce during critical transition stages of their careers due to pregnancy, childbirth, and childrearing. Specifically, the Administrative Supplements to Promote Research Continuity and Retention of NIH Mentored Career Development (K) Award Recipients and Scholars[129] and Administrative Supplement for Continuity of Biomedical and Behavioral Research Among First-Time Recipients of NIH Research Project Grant Awards[130] aim to retain investigators facing critical life events as they transition to the first renewal of their first independent research project grant award or transitioning from career development grants to R01s. In addition, the Research Supplements to

[125] https://acd.od.nih.gov/working-groups/wgd.html
[126] https://grants.nih.gov/grants/guide/pa-files/pa-21-345.html
[127] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-150.html
[128] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-21-010.html
[129] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html
[130] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-055.html

Promote Re-Entry and Re-integration into Health-Related Research Careers[131] provides mentored research training experience for scientists to re-enter or re-integrate into an active research career after an interruption due to family responsibilities or having been adversely affected by unsafe or discriminatory environments. The majority of supplement awardees are women. Finally, two FOAs for the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) were reissued.[132, 133] BIRCWH is a mentored, interdisciplinary, career-development program that connects junior faculty, known as BIRCWH Scholars, to senior faculty with shared research interests in women's health and sex-differences research. To date, over 730 Scholars have been trained through the BIRCWH Program, and most scholars are women.

The Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) program aims to facilitate the transition of promising postdoctoral researchers from diverse backgrounds into independent faculty careers at research-intensive institutions.[134] MOSAIC facilitates a timely transition of promising postdoctoral researchers from diverse backgrounds from their mentored, postdoctoral research positions to independent, tenure-track, or equivalent faculty positions at research-intensive institutions.[135] This exciting new program, launched in 2019, includes two components: an institutionally focused research education cooperative agreement (UE5) and an individual postdoctoral career transition award (K99/R00). The MOSAIC UE5 constitutes awards to independent organizations (such as professional societies) that will support the educational and career development activities of the MOSAIC K99/R00 scholars. Twenty NIH Institutes and Centers are participating in the MOSAIC K99/R00 program.

Inclusive, safe, and supportive environments are the cornerstones to productive, successful research and training and are therefore an NIH-wide priority. Training programs supported by NIGMS are expected to implement robust strategies to ensure that individuals from all backgrounds are welcomed into (and supported by) the biomedical research community. NIGMS has pioneered the incorporation of language into its training grant FOAs to ensure that institutional policies are in place to prevent discrimination, harassment, and other counterproductive practices. Training programs funded by NIGMS are also expected to implement plans to enhance the inclusion, retention, and scientific participation of trainees from all backgrounds.[136]

In FY 2021, NIGMS issued an FOA and a NOSI in the area of interventions research.[137] The FOA encourages applications that propose research designed to test interventions to enhance research-oriented individuals' interest, motivation, persistence, and preparedness for careers in the biomedical research workforce.[138] Funded projects are expected to produce research findings that will guide the

[131] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-134.html
[132] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-21-006.html
[133] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-020.html
[134] https://www.nigms.nih.gov/training/careerdev/Pages/mosaic-scholars.aspx
[135] https://www.nibib.nih.gov/training-careers/training-opportunities/maximizing-opportunities-scientific-and-academic-independent-careers-mosaic-postdoctoral-career-transition-award-promote-diversity-k99r00-independent-clinical-trial-not-allowed
[136] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-20-018.html
[137] https://www.nigms.nih.gov/training/Pages/Interventions.aspx
[138] https://grants.nih.gov/grants/guide/pa-files/par-21-269.html

implementation of interventions in a variety of academic settings and career levels to enhance the diversity of the biomedical research workforce. The NOSI,[139] which was issued with ORWH and several ICs, serves to inform potential applicants of the NIH's interest in supporting research on interventions designed to change the culture to mitigate or eliminate sexual harassment in the biomedical research enterprise.

NIGMS led the solicitation of applications to better understand and address structural racism and discrimination in the biomedical research enterprise. This included issuing a NOSI for applications in 2021 on understanding and addressing the impact of structural racism and discrimination on biomedical career progression and the biomedical research enterprise; one award is forthcoming in FY 2022.[140] NIGMS also issued a NOSI for the creation of training modules to Address Resiliency and Wellness, and Structural Racism and Discrimination in Research Training Environments.[141] NIGMS participated in the NIMHD RFA on Understanding and Addressing the Impact of Structural Racism and Discrimination on Minority Health and Health Disparities[142] and funded an award to study approaches to mitigating structural racism to reduce inequities in sepsis outcomes.

During the first five-year phase (FY 2014-2019), the DPC consisted of three complementary initiatives: Building Infrastructure Leading to Diversity (BUILD), the National Research Mentoring Network (NRMN), and the Coordination and Evaluation Center (CEC). For the second, and final, five-year phase, two initiatives were added: Sponsored Programs Administration Development (SPAD) Program and the DPC Dissemination and Translation Awards (DPC DaTA). The DPC's method of taking a scientific approach to understand training interventions is an innovative design that is likely to serve as a model for biomedical training programs across the nation. The DPC initiatives have already demonstrated considerable progress, including 343 publications resulting from faculty pilot projects and on interventions, development of logic models, short-term and long-term hallmarks of success, site-level and consortium-wide evaluation plans, and consortium governance guidance.[143]

NLM has launched training opportunities aimed at supporting the participation of women in biomedical informatics and data science. In FY 2019, NLM hosted the first women-led codeathon on the NIH campus, which brought together 46 women representing NIH, academia, and the private sector to work collaboratively to address various scientific problems while taking advantage of networking opportunities and instructional sessions.[144] In FY 2020, NLM hosted a special lecture on Gender, Race, and Power in Science, which attracted nearly 1,000 viewers. NLM also established the Ada Lovelace Computational Health Lecture Series to highlight the research of women in computational sciences. Speakers presented talks on topics ranging from Poetical Science for Advancing Health Equity through Information

[139] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-150.html#:~:text=Purpose,in%20the%20biomedical%20research%20enterprise
[140] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-21-033.html
[141] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-22-016.html
[142] https://grants.nih.gov/grants/guide/rfa-files/rfa-md-21-004.html
[143] https://www.nigms.nih.gov/training/dpc
[144] https://infocus.nlm.nih.gov/2019/10/17/women-led-codeathon-a-first-for-nlm/

Visualization, Sequence-Structure-Function Modeling for the 3D Genome, and Dynamic Genome Rearrangements in the ciliate Oxytricha.

A racially and ethnically diverse biomedical workforce is essential for addressing racial and ethnic health disparities, such as those that affect American Indian and Alaska Native (AI/AN) populations. Rates of heart disease and asthma are higher in AI/AN people than in White people, yet AI/AN researchers represent less than one percent of the biomedical work force. To address this issue, NHLBI, NICHD, NIDDK, and NIMHD established the Native American Research Internship (NARI)[145] in 2010 and NARI continues to provide culturally relevant research training and experience for AI/AN students.[146]

NINDS diversity and training programs support awards focused on training and career development in AI/AN communities. Through an initiative for summer research education experiences, [147] NINDS supports Indians Into Medicine: Native Educator University Research Opportunity in Neuroscience, which provides professional development to American Indian tribal school science teachers in North Dakota. The NIH Neuroscience Development for Advancing the Careers of a Diverse Research Workforce program[148] supports the High School Student NeuroResearch Program (HSNRP) that provides research experiences for high school students in Arizona (where 13 percent of their trainees are American Indian), and Undergraduate Readying for Burgeoning Research for American Indian Neuroscientists, which established a cooperative training program between Diné College and the University of Arizona to develop the neuroscience literacy of Diné College Students.

In 2020, NHGRI published a new Strategic Vision for the future of human genomics.[149] One principle laid out in the vision emphasizes the need to champion a diverse genomics workforce because "the promise of genomics cannot be fully achieved without attracting, developing, and retaining a diverse workforce, which includes individuals from groups that are currently underrepresented in the genomics enterprise." To this end, NHGRI developed a 10-year *Building a Diverse Genomics Workforce: An NHGRI Action Agenda*.[150] The objectives of this 'Action Agenda' include both reducing barriers to training opportunities in the field and supporting the development and career progression of researchers from underrepresented backgrounds.

The overarching goal of the NHGRI Diversity Action Plan (DAP) program is to support educational activities that enhance the diversity of the biomedical, behavioral, social, and clinical research workforce in genomics.[151] The DAP has been in place since 2002 and has included over 1,400 participants across 20 projects, increasing the pool of scientists from underrepresented backgrounds trained and poised to enter

[145] https://medicine.utah.edu/pediatrics/research/education/nari
[146] Holsti M, et al. Clin Transl Sci. 2015 Apr;8(2):87-90. PMID: 25588950.
[147] https://www.ninds.nih.gov/funding/training-career-development/high-school-undergraduate-post-baccalaureate/summer-research-experience-high-school-undergraduate-students-and-science-teachers
[148] https://www.ninds.nih.gov/funding/training-career-development/diversity-awards/nih-neuroscience-development-advancing-careers-diverse-research-workforce
[149] Bonham VL and Green ED. *Am J Hum Genet.* 2021 Jan 7;108(1):3-7. PMID: 33417888.
[150] https://www.genome.gov/sites/default/files/media/files/2021-01/NHGRI_DiversityActionAgenda.pdf
[151] https://grants.nih.gov/grants/guide/pa-files/PAR-19-380.html

the genomics workforce. In FY 2020, NHGRI supported 14 DAP grants that developed students' preparedness for graduate school and beyond.

Universities participating in the previously mentioned NLM research training are enrolling predoctoral and postdoctoral fellows and trainees to enhance recruitment of women and other groups underrepresented in biomedical informatics and data science including through partnerships with minority-serving institutions. [152] The funded institutions joined forces and created an annual recruitment and information fair for populations underrepresented in biomedical informatics and data science. In FY 2021, NLM reopened the competition for this training program with a new emphasis on original basic or applied research and encouraged institutions to increase participation of individuals underrepresented in the biomedical, clinical, behavioral, and social sciences research enterprise.

NIBIB's Enhancing Science, Technology, EnginEering, and Math Educational Diversity (ESTEEMED) program supports educational activities that enhance the diversity of the biomedical research workforce through early preparation for undergraduate students in science, technology, engineering, and mathematics (STEM) fields.[153] Each program includes the following components: Summer Bridge Program, Academic Year activities, and a Summer Research Experience. Evaluation of the program is an important component of ESTEEMED so that best practices can be shared with the scientific community.

NIBIB is celebrating the exceptional work of women grantees. The global science community has recognized that a gender gap in STEM has existed for many years. In the past fifteen years, there has been an ongoing effort to promote and inspire women and girls to participate in STEM fields. Research has indicated that gender inequality is partially due to unsupportive cultures that negatively impact the advancement of a woman's career. NIBIB developed a webpage that highlights the career journeys and research endeavors of a selection of these outstanding women researchers.[154]

NIDCR has committed to cultivating a workplace environment in which employees of all backgrounds feel respected, valued, and supported. This achievement will not only improve the organization but enable the NIDCR collective to be better equipped to carry out the mission of oral health for all. NIDCR must overcome unique challenges that differentiate the oral health profession from all other health professions: lack of an adequate pipeline of under-represented minorities who receive dental education and who train as dentists-scientists, dearth of faculty role models in biomedical research and dental public health, and prohibitively high levels of tuition debt and the rising costs of dental education. The Racial and Ethnic Equity Plan (REEP) is a foundational component of the NIDCR's larger intention to build a better sense of belonging within the institute. The tangible outcomes of applied REEP principles and targeted training across groups will broadly address diversity (race, ethnicity, sexual and gender minorities, individuals with disabilities), inclusion, equity, accessibility, anti-harassment, and civility.

[152] https://www.nlm.nih.gov/ep/GrantTrainInstitute.html
[153] https://www.nibib.nih.gov/training-careers/training-opportunities/enhancing-science-technology-engineering-and-math-educational-diversity-esteemed-research-education-experiences-r25
[154] https://www.nibib.nih.gov/science-education/women-science-and-engineering

The North Carolina Women of Color Research Network (NC WoCRN) is a statewide network of researchers representing academia, government, and industry.[155] The network is a product of the NIH Working Group on Women in Biomedical Careers[156] and its Women of Color Research Network (WoCRN). The NIH WoCRN was established to address challenges faced by women and minorities entering and advancing in scientific careers. North Carolina is the second regional chapter established in 2014. The mission of the NC WoCRN is to promote career advancement by broadening participation of women researchers and scientists of color, establishing collaborations and partnerships, multi-level mentoring, outreach, and professional networking. Fully supported by NIEHS and in partnership with academia and industry, the NC WoCRN is an active group that engages its members in professional development activities and events throughout the year, including an annual symposium, webinars, workshops, and social gatherings.[157]

ODSS leads the NIH's Artificial Intelligence/Machine Learning (AI/ML) Consortium to Advance Health Equity and Researcher Diversity (AIM-AHEAD) Program that establishes mutually beneficial and coordinated partnerships to increase the participation and representation of researchers and communities currently underrepresented in the development of AI/ML models.[158] A primary goal is to enhance the capabilities of this emerging technology, beginning with electronic health record (EHR) data.

In 2020, the Environmental influences on Child Health Outcomes (ECHO) Program released a Notice of Special Interest for Research Supplements to Promote Diversity in ECHO Program Research.[159] Inclusion of diverse perspectives can help ECHO better address children's health. The ECHO Program is committed to fostering a diverse workforce, including individuals from groups identified as underrepresented, and is well-poised to support talented individuals from diverse backgrounds. ECHO Cohorts, Cores, and Centers applied for the supplement, through the parent grant, under the stipulations in PA 20-166. The ECHO Program awarded a total of eight supplements to existing grantees. Five of the supplements were for pre-doctoral awardees and three for post-docs. The ECHO Coordinating Center is currently facilitating networking opportunities within ECHO for the supplement awardees.

The NIH HEAL Initiative® supports NIH Research Supplements to Promote Diversity in Health-Related Research (often called diversity supplements).[160] Any HEAL researcher can apply to bring on a trainee or early-stage faculty member, including those from a group underrepresented in research to further that trainee's education and career development. The intent is to enhance diversity in the HEAL workforce from a range of characteristics, which can include, but are not limited to, race and ethnicity, gender, economic/class background, disability, and other features that characterize individuals underrepresented in the biomedical, clinical, behavioral, and social sciences.

[155] https://www.niehs.nih.gov/health/scied/osed/nc_wocrn/index.cfm
[156] https://orwh.od.nih.gov/career-development-education/nih-working-group-on-women-in-biomedical-careers
[157] https://www.niehs.nih.gov/news/events/pastmtg/2021/ncwocrn_2021/index.cfm
[158] https://datascience.nih.gov/artificial-intelligence/aim-ahead
[159] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-098.html
[160] https://heal.nih.gov/research/cross-cutting-research/enhancing-diversity-workforce

NIMH launched a new feature that highlights women who are early-career scientists conducting NIMH-funded research that plays a role in advancing the understanding and treatment of mental illnesses.[161] The campaign is aimed at educating and inspiring young women and girls who may be considering a career in mental health and includes question and answers, social media graphics, quotes, and other tools and resources.

NIMH created the Research Workforce Diversity Program in the Office for Disparities Research and Workforce Diversity (ODWD) to support emerging neuroscientists and mental health researchers from diverse backgrounds through training, mentoring, and funding opportunities.[162] In FY 2019 and 2020, the NIMH Biobehavioral Research Awards for Innovative New Scientists continued to support the career advancement of outstanding, early-career scientists aiming to launch an innovative research program that may transform the understanding, diagnosis, treatment, or prevention of mental disorders.[163] In 2021, NIMH's Mental Health Research Awards for Investigators Early in their Career in Low and Middle-Income Countries (LMICs) continued to support basic, translational, clinical, or services research performed by outstanding scientists in LMICs who are in the early stages of a career in mental health research.[164]

International Workforce Programs

NIH works to expand capacity for research internationally, particularly in LMICs. For example, the Fogarty Emerging Global Leader Career Development Award—with support and collaboration from NCI, NHGRI, NIDCR, NIEHS, NIMH, and NINDS—provides research support and protected time to a scientist who holds an academic junior faculty position or research scientist appointment at an LMIC academic or research institution.[165,166] It is the only career development award available to non-U.S. investigators and provides a pathway to independence for the young investigators trained through Fogarty training programs.

Programs also focus on areas particularly pertinent to the host countries. For example, the HIV-Associated Noncommunicable Diseases Research at LMICs program aims to support locally relevant research in critical areas of HIV-associated noncommunicable diseases at LMIC institutions, to enhance research capacity, and to build a network of researchers both within and across LMICs to address this critical burden.[167]

The Health Professional Education Partnership Initiative complements and enhances the training of a workforce to meet the biomedical, behavioral, and clinical research needs in low-resource, high HIV-burden countries in Africa, including Ethiopia, Kenya, Malawi, Mozambique, Tanzania, Uganda, Zambia, and Zimbabwe.

---

[161] https://www.nimh.nih.gov/research/women-leading-mental-health-research
[162] https://www.nimh.nih.gov/funding/training/programs-to-enhance-workforce-diversity
[163] https://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2021/nimh-biobehavioral-research-awards-for-innovative-new-scientists-nimh-brains
[164] https://www.nimh.nih.gov/news/media/2021/mental-health-research-awards-for-investigators-early-in-their-career-in-low-and-middle-income-countries
[165] https://www.fic.nih.gov/Programs/Pages/emerging-global-leader.aspx
[166] https://grants.nih.gov/grants/guide/pa-files/par-21-251.html
[167] https://www.fic.nih.gov/Programs/Pages/hiv-noncommunicable-diseases-ncds-lmics.aspx

Similarly, the Launching Future Leaders in Global Health Research Training Program is a continuing program that supports one-year mentored research training in global health at established biomedical and health research institutions and project sites in LMICs for U.S. and LMIC pre- and post-doctoral fellows. Fellowship support has been provided to individual trainees by multiple NIH ICOs, helping to build a new generation of global health researchers in a wide variety of fields.[168]

Policies and Activities to Support the Biomedical Research Community

NIH continues to champion an ethical and inclusive research environment. As outlined in the NIH Policies and Procedures for Promoting Scientific Integrity,[169] ensuring the integrity of science and science-based policymaking is at the heart of everything NIH does in fulfilling its mission. By upholding standards of objectivity, fairness, and transparency, NIH assures the public of the credibility of scientific findings. A key component of scientific integrity at NIH is developing and maintaining a diverse and inclusive biomedical workforce pipeline.

Since establishing processes to notify NIH about concerns of sexual harassment affecting an NIH-funded project, NIH has handled extramural harassment allegations involving over 300 individuals.[170] Sexual harassment, as the Advisory Committee to the NIH Director has noted (see page 7 of the report),[171] is only one form of harassment and inappropriate behavior. The committee has also strongly supported using an expanded definition of harassment from the National Academies.[172] Harassment takes many forms including sexual harassment, discrimination, and other forms of inappropriate conduct that can result in a hostile work environment. NIH is committed to promoting safe and respectful work environments that are free from harassment. NIH does not tolerate harassment or discrimination of any kind anywhere NIH-funded activities are conducted.

In order to quickly support research efforts on and the impact of the COVID-19 pandemic, NIH used several different mechanisms of research funding and support for NIH researchers. Of utmost importance to NIH was the health and safety of people involved in NIH research and understanding and controlling for the effects on the biomedical enterprise in the areas affected by the COVID-19 pandemic. To support NIH-funded researchers, NIH offered grant flexibilities by updating guidance for how to address the effects due to the pandemic on productivity when developing grant applications, holding review meetings

---

[168] https://www.fic.nih.gov/Programs/Pages/scholars-fellows-global-health.aspx

[169] https://www.nih.gov/sites/default/files/about-nih/nih-director/testimonies/nih-policies-procedures-promoting-scientific-integrity-2012.pdf

[170] https://nexus.od.nih.gov/all/2021/10/29/expanded-website-outlines-how-to-support-safe-and-respectful-workplaces-at-institutions-that-receive-nih-funding/

[171] Working Group Report to the Advisory Committee to the NIH Director. *Changing The Culture to End Sexual Harassment*. 2019. https://acd.od.nih.gov/documents/presentations/12122019ChangingCulture_Report.pdf

[172] For purposes of the National Academies study, the definition of sexual harassment includes unwanted sexual advances and requests for sexual favors and other unwelcome conduct that is sexual in nature, as well as those situations in which the work or study environment is made intimidating or offensive as a result of actions that are gender-based and that interfere with an individual's academic or work performance, opportunities for advancement, and morale. https://www.nationalacademies.org/our-work/sexual-harassment-in-academia#sectionProjectScope

virtually, having a more flexible stance for accepting late applications, and continuing to offer extensions of funded projects.[173]

NIH recognizes that the high cost of childcare impacts graduate students and post-doctorates funded through NRSA awards, and their ability to successfully complete their training and fully participate in the extramural research workforce. In April 2021, NIH began providing childcare cost support to recipients of full-time NRSA fellowships.[174] In Phase 2 of this initiative, beginning in FY 2022, NIH began providing childcare cost support to full-time predoctoral and postdoctoral trainees appointed on NRSA institutional research training awards.[175] Each full-time predoctoral or postdoctoral NRSA appointed trainee or fellow is eligible to receive $2,500 per budget period for childcare costs provided by a licensed childcare provider. For households where both parents are eligible full-time predoctoral or postdoctoral NRSA trainees, each parent is eligible to receive $2,500. NIH received 229 childcare requests in FY 2021.[176] NIH issued 228 childcare cost awards in FY 2021, totaling $572,083.

In 2020, NIH began piloting two programs[177] to promote research continuity and retention of eligible investigators facing qualifying life events (e.g., pregnancy, childbirth, adoption) at vulnerable career stages.[178,179] The programs provide administrative supplements up to $50,000 in direct costs, plus applicable indirect costs. Flexible use of supplemental funds is highly encouraged to support successful research within the scope of the parent project, including supported effort of additional personnel, computational services, supplies, and equipment to sustain the investigator's research during a critical life event.

The NIH Loan Repayment Programs (LRPs) are a set of programs established by Congress and designed to recruit and retain highly qualified health professionals into biomedical or biobehavioral research careers.[180] The escalating costs of advanced education and training in medicine and clinical specialties are forcing some scientists to abandon their research careers for higher-paying private industry or private practice careers. The LRPs counteract that financial pressure by repaying a researcher's qualified educational debt in return for a commitment to engage in NIH mission-relevant research. Effective for application cycle years 2019-2020, NIH raised the loan repayment award amount from a maximum of $35,000 to a maximum of $50,000 per year. This change, as part of implementing the *21st Century Cures Act*, means that over a two-year new award, talented researchers can now receive a maximum of up to a total of $100,000. LRP awards are also competitively renewable.[181]

[173] https://grants.nih.gov/policy/natural-disasters/corona-virus.htm
[174] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-074.html
[175] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-177.html
[176] https://nexus.od.nih.gov/all/2022/08/10/preliminary-data-on-childcare-cost-support-for-national-research-service-award-nrsa-individual-fellows/
[177] https://grants.nih.gov/grants/policy/nih-family-friendly-initiative.htm
[178] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html
[179] https://grants.nih.gov/grants/guide/notice-files/not-od-20-055.html
[180] https://www.lrp.nih.gov/
[181] https://nexus.od.nih.gov/all/2019/09/20/dont-miss-out-nih-loan-repayment-applications-now-being-accepted/

In 2021, NIH announced a new Extramural Loan Repayment Program subcategory called the Extramural Loan Repayment Program for Research in Emerging Areas Critical to Human Health (LRP-REACH).[182] The objective of the LRP-REACH is to recruit and retain highly qualified health professionals into research careers to pursue major gaps in biomedical and biobehavioral research and/or expand research in emerging areas critical to human health. Emerging areas are considered new areas of biomedical and biobehavioral research that are ripe for targeted investments that can have a transformative relevance and impact for years to come. Although the participating NIH ICs use this mechanism to support early career researchers, each IC will determine which emerging areas of research fit with their IC's research priorities.[183]

The objective of the LRP for Health Disparities Research (LRP-HDR) is to recruit and retain highly qualified health professionals into research careers that focus on minority health disparities or other health disparities. The Program serves as an avenue for NIH to engage and promote the development of research and research programs that reflect the variety of issues and problems associated with disparities in health status. As of September 2019, NIH participation in the LRP-HDR expanded to include all NIH ICs as reviewers and funders of applications consistent with their mission, rather than LRP-HDR applications being assigned to and reviewed by NIMHD.[184]

Assessments of Career Programs and the Scientific Workforce

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

NIH is concerned and mindful about how the COVID-19 pandemic negatively affected the extramural biomedical research workforce. NIH sought to understand the pandemic's effects through formal administrative grants data analyses,[185] two large-scale systematic surveys,[186] and frequent outreach with grant recipient institutions and organizations. NIH recognizes and appreciates that the effects of the pandemic have not been equally felt across all institutions, investigators, and research areas.

NIH saw a marked increase in Research Project Grant (RPG) applications for competing research project grants in FY 2021, leading to a slightly reduced success rate compared to FY 2020.[187] Preliminary FY 2022 data suggest this slightly reduced success rate may have been an aberration, potentially due to the pandemic, and NIH will continue to follow these data closely. The data so far are also not showing any

[182] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-144.html
[183] https://www.lrp.nih.gov/reach-priority-statements
[184] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-137.html
[185] nexus.od.nih.gov/all/2022/04/08/another-look-at-applications-submitted-during-the-pandemic-part-4
[186] nexus.od.nih.gov/all/2021/03/25/the-impact-of-the-covid-19-pandemic-on-the-extramural-scientific-workforce-outcomes-from-an-nih-led-survey
[187] nexus.od.nih.gov/all/2022/03/07/fy-2021-by-the-numbers-extramural-grant-investments-in-research

marked changes in the high-level demographics of designated principal investigators on R01-equivalent and RPG applications submitted before and during the pandemic.[188]

A number of groups and authors have published reports on the effects of the pandemic on biomedical researchers.[189,190,191,192] NIH was aware that, early on in the pandemic, many of its supported laboratories implemented public health mitigation measures, including social distancing. These measures inherently restricted access and severely limited researchers' ability to generate research results and preliminary data. We were aware of concerns about how these measures might disproportionately affect scientists who were earlier in their career, had limited funding, dependent care responsibilities (especially women), faced hiring freezes and other institutional challenges, and were diverted from research activities to clinical care for COVID-19 patients.

NIH conducted two large-scale surveys, one of institutional leaders and one of scientists (opened in the fall of 2020 with results published in March 2021) to objectively document COVID-19's impact.[193] The results provided valuable insights into the well-being of the extramural biomedical research workforce, including as it relates to underrepresented and vulnerable groups. Institutional leaders reported concerns about research functions, research productivity, and financial challenges.[194] Scientists reported concerns about career trajectory, mental well-being, and research productivity.[195]

Most institutional leaders reported implementing COVID-19 monitoring measures, but only a minority provided or expanded facilities for childcare. Scientists reported that key factors affecting their career trajectory included the ability of researchers to apply for grants, caretaking responsibilities, and lost access to research facilities and to collaborators, which together may have adversely affected the ability to generate preliminary data. Parents with young children reported the greatest decreases in research productivity, while women were more likely than men to report that caretaking made it substantially more difficult to complete their work responsibilities.

NIH has taken a number of measures to mitigate the adverse effects of the COVID-19 pandemic on the biomedical research workforce. These include:

---

[188] nexus.od.nih.gov/all/2022/04/08/another-look-at-applications-submitted-during-the-pandemic-part-4
[189] crsreports.congress.gov/product/pdf/R/R46309
[190] www.nature.com/articles/s41562-020-0921-y
[191] www.nature.com/articles/d41586-020-01294-9
[192] genomebiology.biomedcentral.com/articles/10.1186/s13059-020-02031-1
[193] nexus.od.nih.gov/all/2020/10/05/encouraging-participation-in-upcoming-nih-surveys-to-identify-impacts-of-covid-19-on-extramural-research
[194] nexus.od.nih.gov/all/2021/03/25/the-impact-of-the-covid-19-pandemic-on-the-extramural-scientific-workforce-outcomes-from-an-nih-led-survey
[195] The "scientists" who responded to the survey are individual researchers at domestic institutions who logged into eRA Commons within two years prior to the survey, and who identified as having a scientific role (e.g., principal investigators, trainees, sponsors, undergraduate students, graduate students, postdoctoral researchers, scientists, and project personnel).

- Policy flexibilities, including grant award extensions (both funded and unfunded for fellowship and career development awards) to address COVID-19-related research delays.[196]
- Administrative supplements as possible given available funds.
- Automatic one-year extensions of early-stage investigator status for childbirth.[197] In FY 2020, an automatic extension of one year was also implemented for childbirth within the four-year K99 eligibility window.[198]
- Support for early career investigators with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances.[199,200]
- Funding for childcare costs for Ruth L. Kirschstein National Research Service Awards for individual fellows and trainees.[201,202]

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

Every year, NIH reports on NRSA research training outcomes and program management using two GPRA measures that assess the quality of its programs and determine whether substantial numbers of trainees and fellows are retained in research careers. Specifically, NIH compares the proportion of former NRSA trainees and fellows who apply for and receive NIH research grant support with that of their peers. Subsequent NIH support received by these trainees is one of several indicators that reflect the impact of NRSA research training on participants' ability to successfully pursue and sustain a research career. To date, NRSA trainees and fellows have consistently outperformed their counterparts on these measures.

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

Available information regarding postdoctoral scholars participating in the NIGMS Institutional Research and Academic Career Development Awards (IRACDA) career development program[203] indicates that 73 percent of IRACDA alumni are in academic research and/or teaching positions, which is higher than the 43 percent of the overall biomedical workforce going into these positions cited in a 2012 NIH Biomedical Workforce Working Group Report.[204]

---

[196] grants.nih.gov/policy/natural-disasters/corona-virus.htm
[197] grants.nih.gov/grants/guide/notice-files/NOT-OD-18-235.html
[198] grants.nih.gov/grants/guide/pa-files/pa-18-592.html
[199] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html
[200] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-055.html
[201] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-074.html
[202] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-177.html
[203] https://nigms.nih.gov/training/careerdev/Pages/TWDInstRes.aspx
[204] https://acd.od.nih.gov/documents/reports/Biomedical_research_wgreport.pdf

The methods used to monitor and address challenges in the biomedical workforce are also active areas of research. Experts from relevant research disciplines were brought together for a Workshop on Developing a Data Science Competent Environmental Health Science Workforce to examine existing data science and environment, health, and science (EHS) resources, such as the trainee pipelines, availability of mentors, and research, identify how these resources can address EHS-specific training goals in data science, and make recommendations for NIEHS, specifically for training within the field of data science.[205]

NLM conducted an analysis of data scientists' core skills to inform biomedical data scientist training.[206] NLM's research yielded recommendations for a minimal set of core skills for biomedical data scientists that draws on opinions of data scientists, curricula for existing biomedical data science programs, and requirements for biomedical data science jobs. The core competencies included general biomedical subject-matter knowledge, programming language expertise, predictive analytics, modeling, machine learning, team science and scientific communication, and responsible data stewardship.

Historically, biomedical research training focused on preparing all trainees for academic positions: either principal investigators in a research setting or teaching professors. Increasingly, a shift toward preparation for a wider range of career options has emerged. As part of this shift, the NIH Common Fund issued the Broadening Experiences in Scientific Training (BEST) awards to 17 institutions to develop innovative approaches for their trainees to prepare them for a broader expanse of careers in the biomedical research enterprise.[207] The fundamental approach to the BEST awards and early evaluative data collected from the awardees was reported in March 2020.[208]

In FY 2021, NIGMS completed an evaluation of the Native American Research Centers for Health (NARCH) program, which included a formal Tribal Consultation. The evaluation analyzed program outcomes and solicited feedback from various communities, including Tribal Leaders, community members, and Tribal Organizations.[209] Initial evaluation results were presented at the September 2021 NIGMS Advisory Council meeting. Moving forward, the Institute is considering changes to the program to better meet the research, capacity building, and career enhancement needs of AI/AN communities.

The Support for Competitive Research (SCORE) program is a research capacity building program that seeks to increase the research competitiveness of faculty at institutions with limited NIH R01 funding and an explicitly stated mission or historical track records in graduating students from groups nationally underrepresented in biomedical research with B.S./B.A., M.A., M.S. or Ph.D. degrees in biomedical-related sciences. In FY 2020, NIGMS conducted a comprehensive evaluation of the SCORE program;[210] and, as a result, the SCORE program was revised to become the Support for Research Excellence (SuRE) program.

---

[205] https://tools.niehs.nih.gov/conference/datascience_2018/assets/Data_Science_Meeting_Book_v2_508.pdf
[206] Zaringhalam, et al. *Core Skills for Biomedical Data Scientists.* https://www.nlm.nih.gov/od/osi/documents/Core_Skills_Report_final.pdf
[207] https://commonfund.nih.gov/workforce
[208] Lenzi RNL, et al. FASEB J. 2020 Mar;34(3):3570-3582. PMID: 31960495.
[209] https://www.nigms.nih.gov/Research/DRCB/NARCH/Documents/narch-tribal-consultation-report092121.pdf
[210] https://www.nigms.nih.gov/about/dima/Documents/score-panel-presentation-council-01132020.pdf

SuRE is a research capacity building program[211] designed to develop and sustain research excellence in U.S. higher education institutions that receive limited NIH research support and serve students from groups underrepresented in biomedical research[212] with an emphasis on providing students with research opportunities and enriching the research environment at the applicant institutions. It seeks to develop and sustain research excellence of faculty investigators and provide students with research opportunities, while catalyzing institutional research culture and enriching the research environment. Two SuRE R16 programs support investigator-initiated research in the mission areas of all NIH Institutes, Centers, and Offices. A SuRE Resource Center will provide resources to both faculty and offices of sponsored programs at SuRE-eligible institutions.

OAR prioritized expanding the next generation of investigators in the HIV field, in keeping with Goal 4 of the NIH Strategic Plan for HIV and HIV-Related Research, and in support of the NIH Director's focus on expanding the number of ESI/ECI across the NIH.[213] To this end, OAR conducted an HIV Portfolio Analysis for FY 2015-2020 to determine the number of HIV-focused ESI/ECI receiving grants during this period. OAR also organized four Listening Sessions in early 2021 to understand the issues affecting junior HIV researchers. In April-May 2021, OAR convened an Expert Panel composed of 19 senior investigators and mentors to present the findings from the OAR HIV ESI/ECI portfolio analysis and to obtain the panel's input on strategies to enhance the number and diversity of ESI/ECI in the HIV field. In 2021, OAR convened and led a NIH HIV/AIDS Executive Committee (NAEC) ESI Working Group to begin planning for a workshop in Spring 2022.

NINDS officials surveyed 1,479 neuroscientists who had recently obtained a doctorate about their career views.[214] As with earlier studies, results indicated that interest in pursuing a career in academic research dropped as the scientists went through training, especially for women and members of historically underrepresented racial and ethnic groups.[215] Several factors, including lifestyle considerations and a sense of alienation, appeared to contribute to this trend and represent strategic challenges that both NIH policy makers and institutional grantees can address to enhance diversity in neuroscience. Results underscore the needs of women and members of underrepresented groups when training the next generation of neuroscientists.

Focusing on NIH's Workforce

Catalog of Research Training Activities

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

[211] https://nigms.nih.gov/about/overview/Pages/SuRE.aspx
[212] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html
[213] https://www.oar.nih.gov/trans-nih-hiv-research-program/hiv-early-career-resources
[214] https://www.ninds.nih.gov/news-events/press-releases/nih-study-highlights-systemic-diversity-issues-neuroscience-research-community
[215] Ullrich LE, et al. *eNeuro.* 2021 Jun 23;8(3):ENEURO.0163-21.2021. PMID: 34039650.

experience for future investigators, as well as continued professional development of intramural scientists.[216]

As mentioned above, several offices manage research training for the IRP, including the Office of Intramural Training and Education and the Office of Clinical Research Training and Medical Education in the NIH CC. The CC provides a robust array of training resources through the Office of Clinical Research Training and Medical Education. These include training opportunities for students, recent graduates, residents, fellows, and practicing clinicians in areas ranging from pharmacy and bioethics to critical care and imaging, among others.[217]

After completing a terminal degree, individuals may join the IRP as fellows.[218] Fellowship includes programs for clinicians for whom NIH offers opportunities for residency and subspecialty training and accredited graduate medical education programs. For program completion data, see Appendix E.

Figure 5. NIH experts care for a patient in Interventional Radiology at the NIH Clinical Center. Credit: NIH

The Lasker Scholar program is a career development program for independent, tenure-track level clinical researchers. In this unique program, Scholars conduct independent research in the IRP for five to seven years, then have the option of either remaining in the intramural program or leaving for an extramural institution with three years of R00 funding.[219] There have been 38 Scholars since the program's inception in 2012. Half have been women, and seven are members of an underrepresented minority group.

The Earl Stadtman Investigator Search is an annual search for researchers who want to be tenure-track investigators within the NIH Intramural Research Program. It is a national search open to all doctoral-level

[216] https://irp.nih.gov/
[217] https://cc.nih.gov/training/index.html
[218] https://www.training.nih.gov/programs/postdoc_irp
[219] https://www.nih.gov/research-training/lasker-clinical-research-scholars

researchers in any field relevant to the NIH mission. Since its inception in 2009, this search has resulted in over 100 tenure-track hires, many of whom have already achieved tenure. The search typically receives between 400 and 800 applicants per year. The breadth of the search has made it a major contributor to increases in scientific and demographic diversity of NIH intramural tenure-track investigators. In FY 2019, 2020 and 2021, a total of 23 Stadtman Investigators achieved tenure.[220]

Among the IRP's offerings are summer internships for high school, college, and graduate students and year-long engagements for students in graduate or professional school. The Graduate Partnerships Program enables students to pursue research toward their degrees at NIH in partnership with a participating academic institution.[221] The analogous Medical Research Scholars Program provides research-oriented medical, dental, and veterinary students an opportunity to engage in a mentored clinical or translational research project on the NIH campus.[222]

Each IC has developed IRP training in line with its mission. For example, the Rocky Mountain Laboratories–Bethesda Postdoctoral Fellowship Program is a collaborative partnership between NIAID laboratories located in Montana and Maryland. This program fosters scientific exchange and collaboration between NIAID laboratories in different geographic locations while offering a unique postdoctoral training environment. Each fellow has two mentors, one in Montana and one in Maryland, and divides his or her time between the two laboratories while working on a collaborative research project.[223]

The Translational Science Interagency Fellowship (TSIF) program,[224] jointly sponsored by NCATS and FDA, launched in 2021 and aims to provide training in preclinical translational science, technology development, and regulatory research and review. By combining training in translational science and research-related regulatory review, this program will enable fellows to build awareness of regulatory requirements into the early stages of medical product development, improving efficiencies in both the development and review processes. Fellows in this program will develop valuable skills for future careers in academia, the pharmaceutical industry, and government. Three fellows were accepted into the inaugural cohort.

Diversity of the NIH Research Workforce

Several tragic events in 2020 highlighted the nation's struggle with racial injustice, and for NIH specifically, brought needed attention on structural racism within biomedical research. As the world's largest public supporter of biomedical research, NIH aims to set the example on approaches to dismantling systemic challenges and barriers to diversity and equity across the biomedical research enterprise. As part of NIH's commitment to doing all that we can to address these disturbing problems, in February 2021, the NIH-wide UNITE initiative was established to identify and address structural racism within the biomedical research enterprise, as well as bolster the efforts of the NIH offices involved in DEIA. Guided by five committees consisting of staff from across all NIH ICOs, UNITE is committed to ending racial inequities in

[220] https://irp.nih.gov/catalyst/v30i2/meet-26-new-stadtman-investigators
[221] https://www.training.nih.gov/programs/gpp
[222] http://www.cc.nih.gov/training/mrsp/index.html
[223] https://www.niaid.nih.gov/about/rocky-mountain-bethesda
[224] https://ncats.nih.gov/training-education/training/TSIF

the greater scientific community via strategic, short- and long-term actions and funding initiatives that will result in significant, lasting change. The UNITE initiative focuses on three primary areas—Health Disparities/Minority Health/Health Equity Research, internal NIH workforce, and external biomedical research workforce—that intersect and enable greater transparency, accountability, and communications across the NIH and the biomedical research community. The NIH OCPL supported NIH efforts to demonstrate its commitment to ending structural racism through a series of public actions including building and launching the Ending Structural Racism website[225] and the UNITE initiative,[226] supporting the launch of the staff intranet page, hosting Town Halls for NIH staff, promoting it through social media, and more.

The NIH Distinguished Scholars Program (DSP) aims to build a more inclusive community within the NIH IRP by facilitating the recruitment and career development of principal investigators who have a commitment to promoting diversity and inclusion in the biomedical research workforce.[227] The strategy is to recruit cohorts of up to 15 tenure track investigators per year who have both an outstanding record of accomplishments in scientific research and a demonstrated commitment to promoting diversity and inclusion. NIH Distinguished Scholars are supported with research funding as well as with mentoring, professional development, and networking to foster a sense of community and their success as principal investigators. The second cohort in 2019 had 14 scholars, followed by 14 in 2020, and 12 in 2021. From FY 2019 – 2021, 40 scholars have been a part of the program. The cohort of recruited IRP PIs is 58 percent female, 42 percent male, 35 percent White, 25 percent African/African American, 13 percent Hispanic, 20 percent Asian, and 8 percent multi-race. COSWD collaborates with OIR in the leadership of this program.

The COSWD Office created a resource for IC Director/Deputy Director/Scientific Director level personnel, providing access only to faculty data. The IRP Dashboard, as it is known internally, is a visual display of disaggregated demographic data from: (1) NIH's Office of Intramural Research (these are data on investigators at different career levels within the NIH IRP), (2) Association of American Medical Colleges (AAMC) (these are data on medical school faculty), and (3) NSF (these are data on Ph.D. recipients through the Survey of Doctorate Recipients). The IRP Dashboard is a centralized place for workforce demographics, including sex, race/ethnicity, and career level (tenured/senior or tenure-track/junior). The data currently in the IRP Dashboard are from the 2017-2018 timeframe, with updates occurring every two years based on availability from AAMC and NSF (data refresh took place in August 2021). The Dashboard is accessible to IC Director/Deputy Director/Scientific Director level personnel and their staff designees.

The Scientific Workforce Diversity (SWD) Network Platform captures data for all of the NIH SWD diversity and program impact measures and supports the capacity to track and report implementation of strategies, including through the use of Gantt charts. The web based SWD Platform software is simple, intuitive, and user-friendly. In February 2020, the COSWD Office demonstrated the Platform to all of the NIH scientific and clinical directors. Currently, the platform depicts annual data counts and percentages from 2013 through 2019 on race/ethnicity and gender by career level (senior investigators and tenure-track

[225] https://www.nih.gov/ending-structural-racism
[226] https://www.nih.gov/ending-structural-racism/unite
[227] https://diversity.nih.gov/programs-partnerships/dsp

investigators) for 26 IRPs. At the end of FY 2021, COSWD demonstrated the platform for leadership and key staff in 24 of 26 IRPs, with six IRPs using the platform for reporting and managing diversity initiatives.

From 2016 through the end of FY 2021, the COSWD Office developed and implemented a systematic Recruitment Search Protocol[228] for identifying highly qualified, diverse candidates for a range of scientific roles, supporting searches for approximately 40 positions per year, from tenure-track investigators to senior leadership. To broaden the use of this approach, the COSWD Office trained Recruitment Strategists across ICs in use of the protocol. As of October 2021, ICs are expected to take the lead in the use of the protocol, with the COSWD office providing consultation and technical assistance as needed. The COSWD office will continue to utilize the search protocol for high level searches, and to participate in the launch of searches to advise search committees on best practices for inclusive excellence. The COSWD office will also evaluate the impact of the scaled-up recruitment protocol. In FY 2021, COSWD assisted 46 search committees in identifying potential candidates, including 16 Tenure Track/Tenure Eligible, 19 Division Director/Lab Chief level, ten IC Director/Deputy Director, and one Miscellaneous (e.g., Social/Behavioral Scientist). As of the end of FY 2021, COSWD has trained 86 designated Recruitment Strategists or other staff across NIH to serve their respective ICs' searches using the COSWD Recruitment Search Protocol.

COSWD also directs implicit bias education. The educational lectures are delivered to NIH extramural and intramural staff, search committees, and Boards of Scientific Counselors.[229] The purpose is to increase awareness and provide behavioral strategies to minimize the impact of implicit bias on decisions. During FY 2021, COSWD administered an evidence-based Implicit Bias e-Learning, mandatory for NIH-wide staff. The e-learning modules provide foundational training on implicit bias and case examples that enhance the learning experience with scenarios, decision choices, feedback, and implications to support strategies individuals can employ to mitigate implicit bias in various settings. The e-Learning is now publicly available on the COSWD website. COSWD is currently working on enhancing e-learning by incorporating content on establishing psychological safety in the workplace and cultivating employee engagement. In FY 2021, implicit bias education was provided to approximately 40 search committees for scientific investigator and leadership positions. Additionally, the implicit bias e-learning was launched for all NIH staff and made publicly available.

OIR and COSWD established the NIH Equity Committee (NEC) in November 2017 and it remains in progress in April 2022.[230] Convened by the Deputy Director for Intramural Research, the goal of the NEC is to provide feedback and recommendations to the Scientific Directors of each IC's intramural research program in response to detailed reports from them about IC Principal Investigator demographics, activities to improve the research environment for principal investigators who are women and other scientists under-represented in the NIH intramural research workforce (including persons with disabilities), and other steps that have been taken to assure fairness in distribution of resources, salary, and evaluations, in recommendations for advancement, awards, and invitations for seminars, and in mentorship, advocacy, and leadership opportunities. The NEC developed a set of diversity, inclusion, and

[228] https://diversity.nih.gov/programs-partnerships/recruitment-search-protocol
[229] https://diversity.nih.gov/sociocultural-factors/implicit-bias
[230] https://diversity.nih.gov/programs-partnerships/nih-equity-committee

equity metrics and each IC's Scientific Director submits a report of these metrics to the NEC approximately once every two years. Nearly all ICs with intramural research programs have been reviewed at least once and many have been reviewed twice, with several ICs showing improvement in DEIA metrics in the second review.

Since its inception in 2015, the Future Research Leaders Conference (FRLC) has maintained a valuable mission: to attract and provide professional development for exceptional, early-career scientists with a diversity commitment to the IRP.[231] In FY 2021, COSWD enhanced the FRLC program to align with the NIH IRP recruitment objectives, partnering closely with IRP leadership and ICs to design and host a two-day virtual event focused on NIH IRP career pathways. Through five iterations (2021 inclusive), the program has received over 500 applications and selected 145 researchers as Future Research Leaders (FRLs). The FY 2021 program featured 31 selected FRLs—successful early-career scientists representing diverse backgrounds, scientific focus areas, geographic locations, and experience—with over 130 NIH staff attending. During the conference, FRLs participated in sessions to learn career information, showcase their research, and engage on scientific workforce diversity issues. Eleven of the 31 FY 2021 FRLs subsequently applied to the Stadtman Tenure-Track Investigator program.

As part of its efforts to build a data-ready workforce, in FY 2019, NLM launched the Data Science at NLM Training Program, a comprehensive training program intended to help build a workforce for data-driven research and health. This training enables the use of powerful tools and approaches in everyday work and in the conduct, oversight, and management of research. The program featured a variety of all-staff training and networking opportunities, individual training plans, a mentoring program, and courses.

Assessments of Career Programs and the NIH Research Workforce

As part of the NIH Anti-Harassment Program, a Workplace Climate and Harassment Survey was administered in January 2019 to NIH staff including NIH employees, contractors, fellows, and trainees.[232] The survey was designed to be voluntary, confidential, and anonymous. Results from the survey helped in assessing the workplace climate and in identifying elements of NIH's organizational climate associated with harassment. The information provided important context about the NIH workplace and is informing strategies about the development of NIH programs which can improve the workplace moving forward. In addition, the experiences at NIH will inform institutions about approaches they may take to assess and address incivility and harassment in the workplace.

A review of an NCATS intramural translational science training program shows that it equips young scientists with translational science skills leads to early research successes and prepares them for a broad range of science-based careers at the benchtop and beyond.[233] The study evaluated 213 trainees from the NCATS intramural research program, ranging from high school to postdoctoral levels.[234] These alumni have transitioned into a wide array of career functions, types, and sectors. 66 percent of

[231] https://diversity.nih.gov/programs-partnerships/frlc
[232] https://diversity.nih.gov/building-evidence/harassment-survey
[233] https://ncats.nih.gov/news/releases/2020/ncats-translational-science-training-program-sets-young-scientists-on-paths-to-career-success
[234] Haynes B, et al. *CBE Life Sci Educ*. 2020 Dec;19(4):ar51.PMID: 33001768.

postbaccalaureate, 63 percent of pre- and postdoctoral, and eight percent of summer alumni published their research while in the program.

The NIEHS Office of Fellows Development created a tool to track the career paths of postdoctoral fellows in the NIEHS IRP and analyze the data to help science administrators better understand the numerous factors that contribute to career decisions of their fellows.[235,236] The method is the first to standardize categories of career outcomes of NIEHS postdoctoral fellows and separates employment trends in biomedical science by sector, type, and job specifics based on detailed career outcomes from more than 900 NIEHS postdoctoral fellows over the past 15 years.

Science Education and Literacy

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

NIH Activities to Promote Science Education and Literacy

Effectively communicating research results to a broad range of audiences is integral to the scientific process. Promoting science education and literacy not only improves public health and promotes heath equity, but also enhances public engagement with science. The COVID-19 pandemic has highlighted the need for effective science communication. Towards that end, the NIH CEAL Against COVID-19 Disparities aims to provide trustworthy, science-based information through active community engagement and outreach to the people hardest-hit by the COVID-19 pandemic, with the goal of building long-lasting partnerships as well as improving diversity and inclusion in our research response to COVID-19.[237]

MedlinePlus, the National Library of Medicine's authoritative health information resource for patients, families, and the public, is specifically designed to bring trusted information about diseases, conditions, and wellness to the public.[238] Each day, more than one million people turn to MedlinePlus for accurate and reliable health information that is available freely anytime. MedlinePlus usage has steadily increased from more than 300 million users in FY 2018 to more than 400 million users in FY 2021. Available in English and Spanish, MedlinePlus offers information about a broad variety of health conditions, medical tests, drugs and supplements, and (starting in 2019) consumer-focused genetic information via MedlinePlus Genetics. During FY 2019-2021, NLM added or enhanced information on COVID-19 testing and vaccines, mental health, telehealth, and evaluating health information among other topics.

---

[235] https://www.niehs.nih.gov/news/newsroom/releases/2018/january24/index.cfm
[236] Xu H, et al. *Nat Biotechnol* 2018;36(2):197-202. PMID: 29334368.
[237] https://covid19community.nih.gov/
[238] https://medlineplus.gov/

In addition, NLM publishes on behalf of NIH the MedlinePlus magazine. In FY 2021, the magazine migrated to a digital distribution platform, reaching 36,000 subscribers and an average of 250,000 visitors each month, showing consistent growth month-to-month. Print-ready copies of all articles and issues are offered online and individual print copies are made available on request. In June and July 2021, NIH leaders Drs. Francis Collins and Anthony S. Fauci, provided feature stories highlighting NIH and NLM's response to the COVID-19 pandemic.

The Network of the National Library of Medicine (NNLM) partners with local organizations serving underserved populations to deliver community-based skills training in health, digital health, and research literacy. In FY 2021, NLM also issued new awards to seven Regional Medical Libraries to manage the NNLM. Included was support for a coordinating center for NNLM engagement, programs, partnerships, activities, and trainings in support of the NIH *All of Us* Research Program.

NLM intramural researchers are conducting research to identify and remove barriers to finding credible and reliable health information quickly, bridging the gap between trusted health information resources and access to those resources.[239,240] They are employing natural language processing, AI, and deep learning approaches to analyze health data, images, and text.[241] For example, NLM investigators developed an approach to summarize text to address health-related questions asked by the general public.[242] These methodological developments will assist with biomedical information retrieval to answers questions that clinicians, researchers, or the public may have.

NLM's portfolio of exhibitions about Women's Health and Women in Medicine are science communication and education mechanisms that increase the public's awareness of and appreciation for the NLM's trusted health information resources and the Library's wide-ranging biomedical and science collections.[243] Four of these exhibitions, which feature diverse and inspiring inspiriting stories about people, science and medicine, and history, traveled to 43 sites across the U.S. in FY 2019 and 2020.[244,245,246,247] The online adaptations of these educational public exhibitions garnered nearly 160,000 page views. These online exhibition adaptations include NLM health information resources alongside a curated selection of digitized books, images, ephemera, films, and historical documents to enhance and expand online engagement with the public and customers' experiences.[248]

Part of NIGMS' efforts for building research capacity is focused on outreach and education, including during the earliest years in the educational process. Investing in both educators and educational activities

[239] Yadav S, et al. J Biomed Inform. 2022 Apr;128:104040. PMID: 35259544.
[240] Roberts K, et al. J Biomed Inform. 2021 Sep;121:103865. PMID: 34245913.
[241] Goodwin TR, et al. Proc Int Conf Comput Ling. 2020 Dec;2020:5640-5646. PMID: 33293900.
[242] Goodwin TR, Savery ME, Demner-Fushman D. Towards Zero-Shot Conditional Summarization with Adaptive Multi-Task Fine-Tuning. Proc Conf Empir Methods Nat Lang Process. 2020;2020:3215-3226.
[243] https://www.nlm.nih.gov/hmd/about/exhibition/index.html
[244] https://www.nlm.nih.gov/exhibition/careandcustody/index.html
[245] https://www.nlm.nih.gov/exhibition/makingaworldofdifference/index.html
[246] https://www.nlm.nih.gov/exhibition/fiftyyearsago/index.html
[247] https://www.nlm.nih.gov/exhibition/outsideinside/index.html
[248] https://www.nlm.nih.gov/exhibition/so-whats-new/index.html

at the pre-kindergarten to grade 12 level ensures that the nation's biomedical research needs continue to be met. Through the Science Education Partnership Award (SEPA), NIGMS provides opportunities for both students and teachers from various communities (including historically underserved communities) to consider careers in scientific education, research, and practice.[249] Twelve of the 17 SEPAs in IDeA states are currently in partnerships with IDeA COBREs or IDeA Networks of Biomedical Research Excellence (INBREs). These activities and accomplishments place NIGMS within reach of its goal of having at least one SEPA in every state.

NCATS collaborated with The Children's Inn at NIH, the Amateur Radio on the International Space Station (ARISS) and the International Space Station U.S. National Laboratory (ISS National Lab) to host Ask an Astronaut: Biomedical Science Edition.[250] The event took place in September 2019, at The Children's Inn on the NIH Campus in Bethesda, Maryland.[251] This unique experience provided children receiving care at NIH the opportunity to talk to NASA astronaut Nick Hague, who was living aboard the ISS. Participants learned about the importance of conducting biomedical research in a microgravity environment, including NCATS' Tissue Chips in Space projects that had recently completed their first mission to the ISS.

Figure 6: Translational research at the ISS National Lab provides unprecedented opportunities to study the effects of a microgravity environment on the human body. Credit: NASA

[249] https://www.nigms.nih.gov/capacity-building/division-for-research-capacity-building/science-education-partnership-awards-(sepa)
[250] https://ncats.nih.gov/alliances/nasa/ask-an-astronaut
[251] https://www.facebook.com/nih.gov/videos/2498333453576448/

NIBIB's Understanding Medical Scans is a mobile phone application (app) designed to help patients learn what to expect during a medical scan and how scans can help with both diagnosis and treatment.[252] With question-based navigation, images, and videos, this app makes medical imaging information easily available anywhere. It was designed to be understood by the layperson, can give patients basic information about what they are going to experience, and help them ask more informed questions of their technologists. The app is featured in the NIH CC and is available for download on iOS and Android devices.

The Small business Education and Entrepreneurial Development (SEED) Office's Success Stories website contains nearly 100 stories that highlight the health care and economic impact of NIH-funded product development projects.[253] The interactive map allows users to select stories by location, technology type, development stage, or funding Institute. The site also identifies 20 stories highlighting the success of women and minority innovators.

Hands-On Science Education

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

Genome: Unlocking Life's Code immerses visitors in a high-tech environment that captures the revolutionary nature of genomic science.[254] The 4,400-square foot exhibition, which opened in June 2013 at the National Mall, is the product of a partnership between the Smithsonian National Museum of Natural History (NMNH) and NHGRI.[255] After a year at NMNH, the exhibition began to travel to science venues in other states and countries, extending its reach to an even broader audience.

In December 2020, the *All of Us* Research Program began to return genetic results to participants who donated biosamples for research.[256] This reflects the program's priority to give back information to its participants. Initially, participants could choose to receive information about their genetic ancestry and traits. In December 2022, *All of Us* began returning health-related results to participants that chose to receive them.[257] As part of its core values, the program is committed to ensuring that participants have access to their own information.

In 2021, NINR hosted the Methodologies Boot Camp on Artificial Intelligence that explored the impact that AI has in the evolving healthcare environment to improve the care of all patients and families in an

[252] https://www.nibib.nih.gov/Understanding-Medical-Scans-App
[253] https://seed.nih.gov/portfolio/stories
[254] https://www.unlockinglifescode.org/
[255] https://www.genome.gov/outreach/unlocking-lifes-code-exhibition
[256] https://allofus.nih.gov/news-events/announcements/nihs-all-us-research-program-returns-first-genetic-results-participants
[257] https://allofus.nih.gov/news-events/announcements/nihs-all-us-research-program-returns-genetic-health-related-results-participants

equitable way.[258] The goal was to showcase how AI can improve outcomes and how to avoid unintended consequences that increase disparities. Participants explored the role of AI in promoting health and preventing illness, and discussed strategies to build partnerships and collaborations among clinicians and scientists, as well as gain a better understanding of the potential for AI to reduce disparities and identify strategies to detect and prevent bias in health-related algorithms. Participants also analyzed prevention, clinical, and translational AI applications to enhance quality of programs, policies, and care to reduce health disparities and increase health equity.

Summary

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

[258] https://www.ninr.nih.gov/newsandinformation/newsandnotes/bootcamp2021video

Chapter 2 Overview of NIH Research

Introduction

In pursuit of its mission, NIH conducts and supports biomedical, behavioral, and social science 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 that is designed to understand the basic causes and mechanisms of disease, find new ways of identifying, preventing, and treating disease processes, and bring these new interventions into common practice for the public benefit.

Figure 7. NIH supports the full continuum of biomedical research.

The continuum, from basic research to practice, is summarized below and illustrated in Figure 7. NIH activities that relate to each stage of this continuum are then described in more detail in subsequent sections of this chapter. It should be noted that the path from basic research to clinical and community practice is not a continuum in the strictest sense because all stages of biomedical, behavioral, and social science 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 7).

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 biomedical research and a central feature of the NIH research program.

Preclinical Translational Research

Realizing the benefits of fundamental biomedical discoveries depends on the translation of knowledge into the development of new diagnostics, therapeutics, and preventive measures. NIH is a key supporter of preclinical translational research—studies that serve as a bridge between basic research and human

medicine. Early translational investigations are often conducted 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 therapeutics.

Clinical Research

Medical advances arise from rigorous testing of new strategies for recognizing and intervening in disease processes, whether the intervention occurs before the processes manifest (prevention) or after disease pathogenesis (treatment). Clinical research[259] is conducted with human volunteers and includes patient-oriented studies, such as clinical trials, to determine if a given intervention is both safe and effective.[260]

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: patients, families, health care providers, and the broader public health community. The postclinical translational stage takes results from clinical studies

---

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

(1) Patient-oriented research: Research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that use human tissues that cannot be linked to a living individual. Patient-oriented research also 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.

[260] Clinical trials are defined by NIH as follows: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

- See Common Rule definition of research at 45 CFR 46.102(l).
- See Common Rule definition of human subject at 45 CFR 46.102(e).
- The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
- An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies.
- Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and positive or negative changes to quality of life.

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html
https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46/subpart-A/section-46.102

and investigates the best methods to implement those results for broad application. NIH supports postclinical translational research to identify factors that enhance access to and implementation of new interventions, with the aim of optimizing the health care delivery system to reflect the latest medical advances.[261] Studies in this area include the development and testing of novel models and methods to best implement newly discovered interventions to reach diverse groups and populations (e.g., racial and ethnic groups, rural populations).

Clinical and Community Practice

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

Feedback Between Different Stages of the Research Continuum

The course of NIH research is not a true continuum, in that it does not necessarily progress in series, 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, in turn, addresses the feasibility of the strategies and informs 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, and environmental circumstances. These studies stimulate research to understand the mechanisms of disease and to develop methods of diagnosis, prevention or intervention. An overview of NIH's focus on epidemiological research is provided later in this chapter. The NIH research continuum also requires investment in research resources and infrastructure, as well as the development of new technologies, as described at the end of this chapter.

Basic Research

Basic research focuses on uncovering the fundamental principles of biology and behavior, as well as on understanding the basis of health and disease, which drives progress in biomedical and behavioral sciences from the bottom up. Investments in basic research lay the foundation for clinical discovery and yield inestimable rewards and benefits to public health, from the incremental advances in our

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

understanding of a biological process and how it might err in a given disease, to the groundbreaking discoveries that revolutionize our approaches to treating or preventing that disease.

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 the ways in which finely tuned biological and behavioral processes work together in harmony, and how these processes can break down and form the basis of disease. 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. And 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 interaction among research groups across multiple scientific 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 center 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 all ICs across NIH, and progress often requires interdisciplinary approaches to develop new technologies, improve methods of data analysis, and provide insight on fundamental disease pathways. In this endeavor, NIH fosters collaborations that span all the traditional and emerging disciplines of the life, physical, engineering, computer, behavioral, and social sciences. Several of the key NIH basic research fields are outlined below, and 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," which are easier to work with and exist in precisely defined, controlled settings. NIH supports the development of a wide range of research models, including those individual studies that use model organisms.

Basic research using model systems and organisms has provided foundational knowledge about human growth and development, behavior, maintenance of health, and development of disease. Research in such model systems—on bacteria, yeast, insects, worms, fish, rodents, primates, and even plants—has shown

that many of the basic operating principles are nearly the same in all living organisms. Therefore, a finding made in research on fruit flies or mice may shed light on a biological process in humans and lead to new methods for maintaining human health and in diagnosing and treating disease.

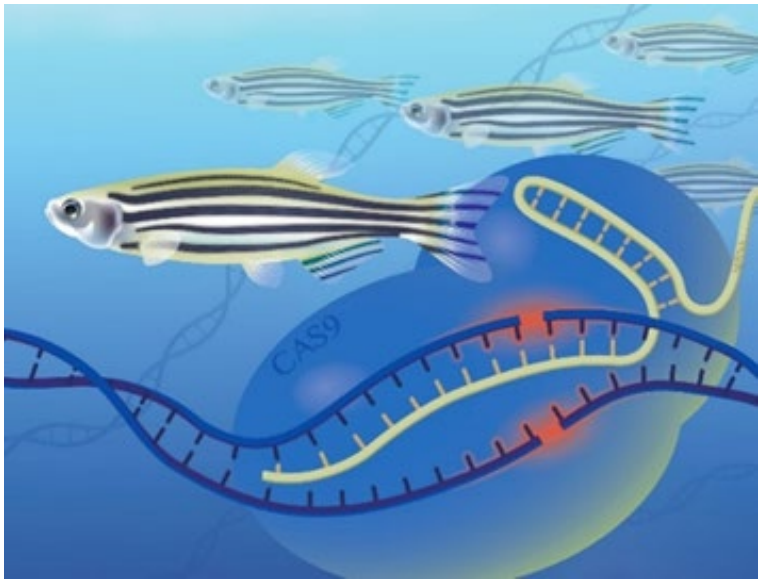


Figure 8. NHGRI scientists are homing in on specific genes in zebrafish to help them better understand the function of genes in people. Credit: Darryl Leja, NHGRI

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

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

Figure 9. At the largest zebrafish facility in the country, Kevin Bishop, an NHGRI Zebrafish core staff member, holds up a tank of zebrafish to observe their behavior and physiology. Using molecular techniques, researchers alter the zebrafish's genome to mimic what is seen in human patients in the clinic. Credit: Ernesto del Aguila III, NHGRI

Cell Biology and Molecular Mechanisms

In the human body, all biological components—from individual genes to entire organs—work together to promote normal development and sustain health. This biological teamwork is made possible by complex molecular machinery that carries out the function of cells along 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 such 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 disorders.

Human growth and development are lifelong processes that have many phases and functions. Most 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. Most life processes exist in a balance, and when the biochemical choreography of cells goes awry, that balance is lost, affecting bodily health. Glitches in the cell cycle can lead to a host of diseases, most notably cancer, which can be defined as uncontrolled cell division and the failure of programmed cell death. Scientists have been taking advantage of the wealth of basic research on the cell cycle to develop anticancer drugs that aim to bolster or block the cell cycle of molecules.

Characterizing Cellular Molecules

Omics approaches (e.g., genomics, proteomics, metabolomics) characterize cellular molecules as genes, proteins, metabolites, carbohydrates, and lipids, and such approaches 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 just a decade ago would have taken months, if not years. Similarly, the speed of sequencing the genome has increased, propelled further by the decrease in sequencing costs over time.

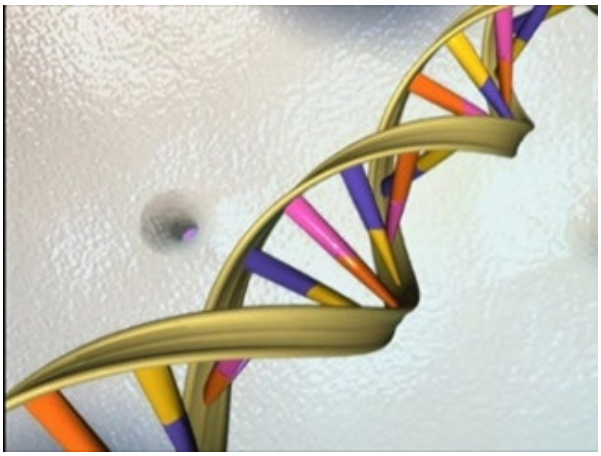


Figure 10. DNA double helix. Credit: NHGRI

These advances have led to the accumulation of large datasets that scientists mine using statistical methods, or bioinformatics, to better understand how networks of cellular components function in concert to produce a state of normal health, and to identify the key players that can go awry as either a cause or a result of disease. For example, scientists 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 they will compare the proteome (the entire complement of proteins) of a specific cell type with those of another (e.g., Alzheimer's brain cells versus normal brain cells). The deluge of resulting information has, in turn, generated a pressing need for specialized tools to view and analyze the data, and for computerized databases to store, organize, and index the data. NIH's approach to this is discussed below under Infrastructure, Research Resources, and Technology Development.

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 the organism's development, physiology, and any disease. With a map of the human genome now available, NIH continues to support research to further understand how variations in the genetic sequence among individuals may contribute to health and disease.

Genetic analyses, such as genome-wide association studies (GWAS), exome sequencing, and whole-genome sequencing, allow researchers to identify inherited genetic differences, referred to as variants. In turn, these variants may be associated with traits conferring increased risk or protection for specific diseases and disorders. For example, GWAS often compare the entire genome (the entirety of the genetic material) of individuals with a given trait, with that of individuals who do not have that trait.

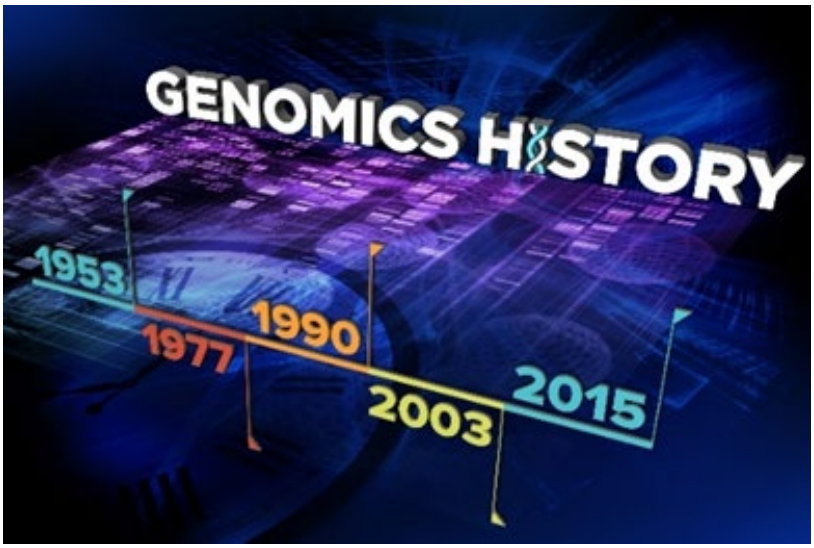


Figure 11. Timeline of our genomics history. For more information, visit NHGRI's History of Genomics Program.[262] Credit: Ernesto Del Aguila III, NHGRI

Genomic research focuses not just on individual genes but also on the functioning of the entire genome as a network and, as important, 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.[263]

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, specifically changes that disrupt the function of the protein they encode.

Many health conditions, including common ones such as heart disease and diabetes, are influenced by multiple genes in combination with environmental factors. However, in most diseases, the role of genes and the environment is more complicated. Some diseases arise as a result of spontaneous gene mutations that occur during a person's lifetime. Others are caused by complex cascades of changes in gene expression that is triggered, perhaps, by environmental factors. DNA is composed of four chemical building blocks (bases), and because the biological information encoded within DNA is determined by the

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

order of those bases, differences as small as one base in our three billion pairs of DNA bases can cause disease directly, or can cause a person to respond differently to particular pathogens or drugs.

Multiple genetic and environmental factors play a role in myriad common diseases and disorders, and while not all the genetic risk factors are fully understood, NIH researchers have begun to identify individual genes or regions of DNA associated with particular conditions. Due to the overwhelming influence of the genome on human health, almost every NIH IC now engages in genome-related research.

Epigenomics

Although an organism's genetic composition is an important determinant of health and disease, additional mechanisms are involved in interpreting the genome and in 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, independent of the DNA sequence, influence whether genes are active or silent.

Epigenetic processes control normal growth and development and, in diseases like cancer, are disrupted. Furthermore, such factors as diet and exposure to environmental chemicals throughout all stages of human development can cause epigenetic changes that may turn certain genes on or off. Research in animal models has revealed that even particular parenting behaviors trigger epigenetic changes and alterations in the physiological and behavioral functioning of offspring. Changes in genes that would normally protect against a disease could make people with those altered genes more susceptible to developing that disease later in life. Researchers also believe some epigenetic changes can be passed from generation to generation.

Translating the Genetic Code: Transcriptomics, Proteomics, and Metabolomics

Beyond understanding genes and their regulation, NIH also supports investigators in the fields of transcriptomics, proteomics, and metabolomics. Transcriptomics research involves systemwide studies to understand which genes are turned on or off and when. Genes code for the proteins that carry out almost all cellular functions, so proteomics focuses on understanding which genes are active and, by extension, the catalog of proteins carrying out cellular functions in a given cell type under particular sets of conditions. This knowledge provides a picture of the molecular players involved in health and disease. In addition to understanding the collective composition of proteins in a cell, researchers also aim to characterize the proteins' three-dimensional structures. In the field of metabolomics, researchers use 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 the additional molecular compounds associated with cellular function. In glycomics, researchers seek to better understand the role of glycans (complex chains of sugar molecules) in various cellular functions. Glycans, which are often found attached to the surface of cells and to proteins

on the cell surface, serve important roles in inflammation, heart disease, immune defects, neural development, and cancer. To advance the field of glycomics, NIH supports programs that develop technologies for the analysis of glycans in complex biological systems, and NIH has established the Consortium for Functional Glycomics,[264] which provides access to a technological infrastructure for glycobiology in support of basic research.

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 compile all this information across multiple scales, however, researchers must integrate experimental data with computational approaches that generate models to describe complex biological systems. Here NIH researchers are leading the way, pioneering the field of systems biology, which draws on biology, mathematics, engineering, and the physical sciences. In addition to describing the interactions among genes, proteins, and metabolites, system biology models are intended to predict physiological behavior in response to natural and artificial perturbations. By monitoring the effects of a perturbation in virtual experiments, scientists can generate hypotheses that can then be tested in cellular systems or model organisms to gain a better understanding of the molecular contributions to normal health and disease.

Basic Behavioral and Social Science Research

Considering 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 the approaches that are essential for understanding individual and collective systems of behavior and psychosocial functioning. The research is used in predicting, preventing, and controlling illness, as well as in developing more personalized (tailored) interventions. It is also applied in enhancing adherence to treatment and minimizing the collateral impact of disease, as well as in promoting optimal health and well-being across the lifespan and over generations.

Basic behavioral and social sciences research supported by NIH includes studies 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 research related to economics and decision-making is yielding findings that can be translated into effective interventions to change behavior and improve health. In addition, basic behavioral research on social networks is improving our understanding of how smoking and obesity spread through socially connected individuals, and it is providing insight into how these networks might be used to transmit healthy behaviors.

Biopsychosocial research looks at the interaction among biological, psychological, and social processes, and it includes research on gene-environment interactions and other biobehavioral processes. Research

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

in this area examines 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 as 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 the impact of the variables on the behavior of the system as a whole over time.

Other External Factors That Influence Human Health and Disease

NIH supports basic research to understand how environmental factors influence the development and progression of human diseases. The environment includes all physical, chemical, and biological factors external to the person, as well as substances—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 will be 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. For example, NIH recently launched the Climate Change and Health Initiative, a cross-cutting effort to reduce health threats from climate change across the lifespan and build health resilience in individuals, communities, and nations around the world, especially among those at highest risk.[265]

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 indicated by the fact that less than one percent of compounds that are initially tested ever make their way into medicine cabinets. The development and adoption 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 that surface in basic research fail to become proven strategies to address health, often failing in the preclinical stage.

Now, however, advances in biomedical research and technologies have created unprecedented opportunities to transform the translational development pipeline, especially in the preclinical stage.

[265] https://www.nih.gov/climateandhealth

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

NIH is 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 that of others.

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

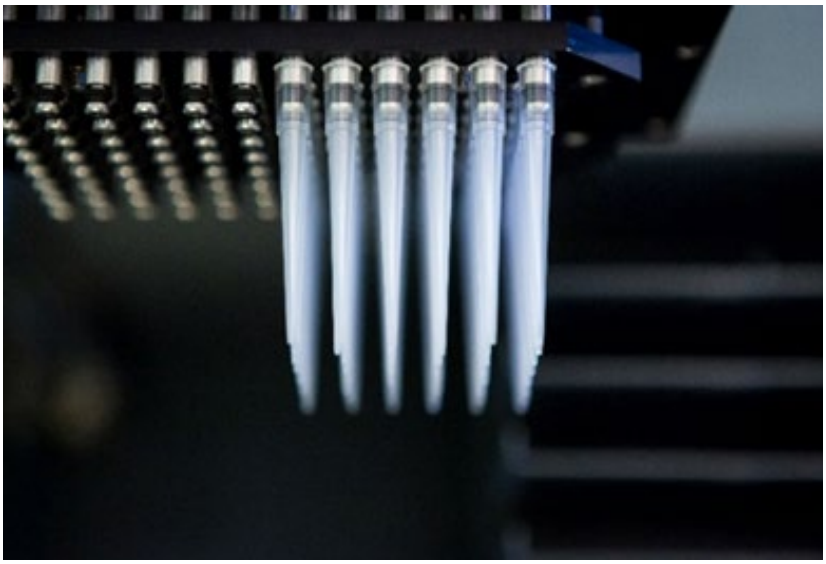


Figure 12. Automated sample handling equipment used in high-throughput in vitro absorption, distribution, metabolism, and excretion assays at NCATS' Drug Metabolism and Pharmacokinetics laboratory. Credit: Daniel Soñé Photography

This is an exciting time for the advancement of translational science and the increasing speed of the 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 are within reach, as are the identification of new targets and pathways for the development of novel therapeutics. Coupled with these advances, progress in technology and other fields of biomedical research has advanced the potential for the development of new diagnostics and treatments for a wide range of diseases, presenting opportunities 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 volunteers and includes patient-oriented research, such as clinical trials, as well as behavioral and observational studies and outcomes research.

NIH supports many types of clinical trials. These are a crucial subset of clinical research, where trials are 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 be designed to examine numerous different topics: experimental drugs, biologics, or devices; new combinations of drugs or biologics; innovative approaches to surgery or radiation therapy; use of new biological products, such as gene therapy; or behavioral interventions, such as exercise training or medication adherence. Prevention trials look for better ways to prevent a disease or to keep it from returning, and they may incorporate research approaches that assess medicines, vaccines, and lifestyle changes, among other interventions. Screening and diagnostic studies are used to find better ways to detect or diagnose diseases or conditions, and quality-of-life trials (or supportive care trials) explore ways to improve people's ability to continue their activities of daily life, even as they manage chronic illnesses or approach the end of life. NIH ICs oversee a broad portfolio of clinical research that encompasses both intramural and extramural programs.

Clinical Resources and Programs

The goal of the NCATS Clinical and Translational Science Awards (CTSA) program 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 those research resources that local and national research communities need to improve quality and efficiency across the translational research continuum.[266] 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 (CC)

As mentioned in Chapter 1, the NIH CC is typically 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 research achievements, such as the development of chemotherapy for cancer, the first use of

[266] https://ncats.nih.gov/ctsa

an immunotoxin to treat a malignancy (hairy cell leukemia), and the identification of the genes that cause kidney cancer, which led to the development of six new, targeted treatments for advanced kidney cancer. The CC and partners also participated in demonstrating that lithium helps depression, the first gene therapy, the first treatment for AIDS (with the antiretroviral drug azidothymidine), and in the development of tests to detect HIV and hepatitis viruses in blood, which led to a safer blood supply.

Figure 13. CT scans are an important tool in patient diagnosis and treatment. Since 2014, this CT scanner in the NIH Clinical Center has provided patients and researchers with better quality scans, faster run times, and a lower radiation dose. Credit: NIH

Investigators outside the NIH campus can access the CC's research resources through a program that fosters collaboration with the NIH IRP on projects related to the translation of basic biological discoveries into clinical applications that improve health. This program provides access for external researchers to the CC, and thus leverages the diverse CC resources, expertise, and infrastructure to support studies that may not be readily supported elsewhere.[267]

Institute and Center Clinical Research Activities

Nearly all of the NIH ICs support a combination of resources, programs, and initiatives targeted at strengthening and expanding clinical research. Clinical testing of novel therapies is critically important to patients because it can lead to the development of new treatments, and for professionals because it can advance 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 infrastructure must be established, and protocols must be approved.

[267] https://www.cc.nih.gov/researchers/resources.html

ClinicalTrials.gov

Launched in 2000, NIH's *ClinicalTrials.gov* is the largest, most frequently used public clinical trial registry and results database in the world.[268] Developed and operated by NLM in response to Congressional legislation, it provides patients, family members, health care professionals, clinical researchers, and members of the public with access to information about clinical trials that touch on a wide range of diseases and conditions. The registry offers users multiple functionalities. They can 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). Site users can also track the progress of a study from initiation to completion, and for a subset of registered trials, they can obtain a summary of research results. The unique identifier assigned by *ClinicalTrials.gov* to each registered trial has become a de facto professional standard for identifying clinical trials and is widely and routinely used in communicating the results of such trials. By the end of FY 2021, ClinicalTrials.gov contained registration information for 390,947 studies and results summaries for 56,731 registered studies.

Participation in Clinical Trials

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

- Many doctors do not suggest clinical research studies to their patients.
- Some individuals may not realize the number of possible ways they can contribute to research other than as a patient (e.g., as healthy participants or taking a survey online).
- People may not realize they can volunteer directly to be participants in clinical research.
- Stigma may complicate 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, or 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.
- Information about a trial may be too technical to be easily understood, and forms (consent documents, etc.) may be too complicated for some individuals to understand and complete.
- Individuals may face any number of logistical challenges, such as transportation, childcare, or constraints on time away 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. They are stressing the importance of NIH-supported clinical research to public health, the pressing need for clinical trial participants, and the benefits of clinical trial participation for public health.

[268] https://clinicaltrials.gov/

To further broaden participation in biomedical research, NIH developed an important educational website called NIH Clinical Research Trials and You[269] to help people learn more about clinical trials, why clinical trials matter, and how to participate. The site features information about participating in clinical trials, as well as stories of firsthand experience from clinical trial volunteers, along with explanations from researchers of purpose and what to expect during a clinical trial. The website also includes links for locating and enrolling in programs, directing site users to review the trials that are posted on ClinicalTrials.gov, and to look at the trial registries maintained by NIH ICs.

Health care professionals can use the site to learn about evidence-based strategies for talking with patients about trials, print audience-tested posters to help promote trials in their practices, and find other clinical trial educational materials. To ensure that physicians are aware of their critical role in clinical trial recruitment, NIH communications offices are working to increase coordination with physicians and other health providers in the community, taking advantage of social media tools to raise physician awareness about clinical research.

Furthermore, OCPL has developed an equivalent Spanish-language version of the site (Investigación Clínica[270]), which is designed to introduce Spanish-speaking individuals to NIH clinical research, and which also supports NIH compliance with federal language access requirements.

Collaborations and partnerships with community members involved in or affected by NIH research are valuable to all, so NIH also leverages the NIH Clinical Research Trials and You website to develop partnerships with NIH grantees and other interested parties. All these efforts also assist with NIH's comprehensive awareness-building initiative.

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

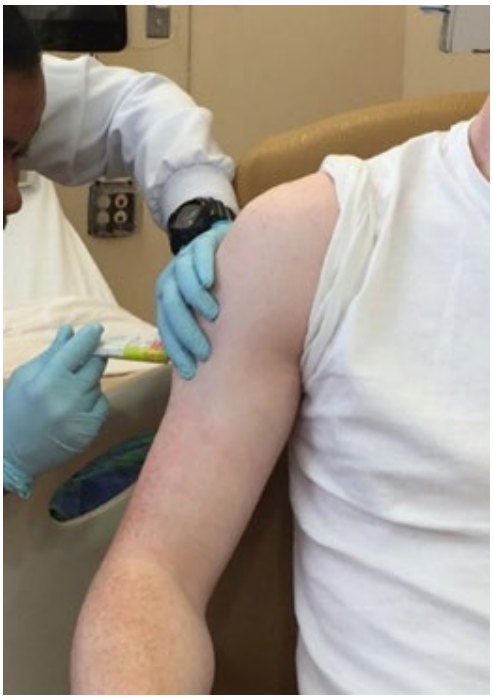


Figure 14. A participant receives an injection in an NIH trial examining a vaccine intended to provide broad protection against a range of mosquito-borne diseases. Credit: NIAID

Inclusion of Women and Minorities in Clinical Research

Health experts have identified a phenomenon called the "efficacy–effectiveness gap," which 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) helps ensure that research findings can be generalizable to the entire population by requiring that all NIH-funded clinical research include women and members of minority groups, when appropriate to the proposed research. Additionally, the statute requires clinical trials to be designed to analyze whether study outcomes differ for women and members of racial and ethnic minority groups from those results relating to White males. 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*.[271]

In accordance with this policy, funding applicants are required to describe the populations that will be included in a proposed study, to justify any exclusion of specific groups, and to provide planned enrollment information. Scientific review groups at NIH assess proposed clinical research studies for the inclusion (or exclusion) of individuals on the basis of sex, gender, race, and ethnicity, as well as for the inclusion (or exclusion) of individuals across the lifespan, to determine whether the study is justified in terms of its scientific goals and the proposed research strategy. Investigators also must report their cumulative enrollment annually, parsing the data by sex, gender, race, and ethnicity of participants.

[271] http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Inclusion enrollment data are reported in aggregate in *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research* (see Appendix F).[272]

Postclinical Translational Research

Postclinical translational research investigates methods for ensuring that evidence-based interventions are broadly applied and accessible to those who need them the most. HHS pursues this effort primarily through its support of health services research. Health services research is a multidisciplinary field, with both basic and applied methodologies that examine 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. Within HHS, AHRQ has primary responsibility for health services research.[273]

NIH also plays a significant role in supporting health services research across the government by focusing on questions specific to the missions of each IC. For example, NINR supported observational studies on the relationship between patient-to-nurse hospital staffing ratios and patient odds of in-hospital mortality and hospital readmission.[274] Similarly, NIAID supported studies that showed that cleaning patients with an antiseptic solution as well as the targeted use of a nasal antibiotic greatly reduced bloodstream infections and antibiotic-resistant bacteria in hospitalized patients with medical devices.[275] However, in general, NIH funds health services research in which health outcomes and health-related behaviors are the primary focus and the connection between the subject(s) of the study and improved understanding of health are explicit.

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

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

[272] https://report.nih.gov/research/inclusion-women-and-minorities-clinical-research#/
[273] https://www.ahrq.gov/cpi/about/mission/index.html
[274] Lasater KB, et al. *Med Care.* 2021 May 1;59(5):444-450. PMID: 33655903.
[275] Huang SS, et al. Lancet. 2019 Mar 23;393(10177):1205-1215. PMID: 30850112.

available through health care delivery organizations, such as the electronic medical records of thousands of patients. A number of NIH Institutes already support collaborative activities among various health care delivery organizations, such as health maintenance organizations and biomedical researchers, to implement large studies with real-world benefits.

Disseminating and Implementing Clinical Research Discoveries

Dissemination and implementation research is intended to bridge the gap between clinical research and everyday practice by building a knowledge base that addresses how health information, interventions, and new clinical practices are transmitted and translated for use in public health and health care service.

NIH routinely partners with other federal agencies to ensure that the evidence produced at NIH is understood and so has the best chance of informing health efforts and contributing to policy and procedural changes at other federal agencies. This helps highlight the benefits to all who are involved in these collaborative partnerships. 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 identify 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 goal of improving health outcomes. NIH communications efforts that focus on the translation and dissemination of this information to hospitals, doctors' offices, and community settings are key to ensuring that patients reap the benefits of NIH-funded research.

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

Disseminating Health Information

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

For example, the *NIH MedlinePlus* magazine and its Spanish-language counterpart *NIH MedlinePlus Revista* are quarterly consumer magazines that bring the latest clinical findings directly to patients and their families. The magazines complement the *MedlinePlus*[276] and *MedlinePlus en español*[277] websites (both of which were developed and are maintained by NLM) and offer trusted, consumer-oriented health information on more than 975 health topics.

[276] http://www.nlm.nih.gov/medlineplus/
[277] http://www.nlm.nih.gov/medlineplus/spanish/medlineplus.html

To complement the websites, NIH has developed MedlinePlus Connect,[278] which is available free to health organizations and providers. This web application provides access to MedlinePlus resources by using direct links from EHRs, patient portals, and other health information (IT) systems. Queries sent through MedlinePlus Connect are based on diagnosis, procedure, and related medical codes, and return information from *MedlinePlus* to patients and providers immediately, at the point of care. In addition, NLM's NNLM improves access to health information for all by offering training to support the effective use of NLM information resources by librarians, health professionals, researchers, and the public.

A monthly public-facing digital newsletter from OCPL, *NIH News in Health,*[279] offers subscribers practical, clear, and to-the-point health news and tips based on the latest NIH research. The NIH online *Health Information Portal*[280] is a user point of entry that guides people to relevant, timely health resources from the entire NIH website. Together, these online solutions bring the most recent, vetted health information directly to the public in an accessible, user-friendly format. OCPL also maintains the website *NIH Research Matters*,[281] which highlights research accomplishments by NIH and NIH-funded scientists, which seeks to improve public understanding of current science by offering links to a compendium of stories related to NIH research in an accessible, blog-like format. Additionally, OCPL launched a Spanish-language health information website, *Portal de Información de Salud de NIH,*[282] which offers evidence-based health information from across NIH on topics ranging from child health to aging. The mobile-friendly site includes translations of many health articles from *NIH News in Health*.

NIH also continues to broaden its social media presence, using various popular and current outlets, employing 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*[283] continues to enhance and broaden the agency's national and international profile. The blog builds on NIH's existing awareness and education efforts, focusing on the public's participation in NIH-funded research and the public's understanding of the value of—and return on—government-funded medical research. This widely read blog, which features news and imagery that reflects cutting-edge science and offers opportunities for public feedback, reflects the importance that NIH places on telling the NIH story through all forms of media.

However, simply communicating scientific breakthroughs, research results, and the availability of new treatments does not assure that these will be adopted in common medical practice, nor does it ensure that this information will be used to inform policymaking. So, in addition to its communications efforts, NIH works with numerous partners to bring NIH research into clinical and community practice, focusing on both treatment and prevention, and into the policymaking that affects public health. These partnerships include those agencies that are engaged in improving health and reducing the burdens of disease within HHS (e.g., FDA, CDC, AHRQ) and from across the U.S. government, such as the VA and the U.S. Department of Defense (DoD). NIH also partners with other, nongovernmental agencies, scientific

[278] https://www.nlm.nih.gov/medlineplus/connect/overview.html
[279] https://newsinhealth.nih.gov/home
[280] https://www.nih.gov/health-information
[281] https://www.nih.gov/news-events/nih-research-matters
[282] http://salud.nih.gov/
[283] https://directorsblog.nih.gov/

organizations, patient advocacy groups, and health care delivery systems. These partnerships further support the broader uptake into clinical and health care settings of the latest NIH research findings and evidence.

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, targeting a variety of audiences.

Many of these campaigns focus on specific audiences to fortify prevention and treatment efforts. Others concentrate on one of any number of specific health outcomes, including: 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 online 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 can be found on the NIH website.[284]

Identifying Public Health Needs (Epidemiology)

To achieve its mission, NIH must address both ongoing and emerging public health needs. NIH investments in epidemiology and public health continue to pay off as NIH contributes to the nation's ability to quickly detect emerging and re-emerging diseases and mitigate their health impacts, thus improving the nation's resilience to future disease threats.

NIH Epidemiological Research Activities

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

Population Studies

Population studies are a type of epidemiological research aimed at better understanding how populations change in size, composition, and distribution. They look at the complex social, economic, and cultural

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

factors that cause such changes, and at the consequences for health and well-being at both the individual and societal levels when a population changes. The population-based perspective provided by such studies often helps establish a foundation for the practical application of scientific knowledge, including spurring change in clinical practice and the development of public policy. For example, the Framingham Heart Study, which was initiated in 1948, linked the risk of cardiovascular disease to such factors as high serum cholesterol levels, hypertension, and cigarette smoking. From these results, clinicians were able not only to identify patients at high risk for cardiovascular disease but—even more important—to develop interventions to reduce risk.

Epidemiological Studies in Diverse Contexts

A comprehensive understanding of health and disease requires consideration of factors from the molecular level to the community level. Conducting studies in diverse contexts helps clarify how these contributors converge to influence health, and that diversity 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). NIH also supports research on social determinants of health, with a Research Coordinating Committee and Executive Committee dedicated to supporting and strengthening a research portfolio on social determinants of health within the larger NIH biomedical enterprise.

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 application than those currently available. NIH makes significant investment in the development of research infrastructure and resources, as well as in 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 continuously updated, as resources become available. Examples of NIH-funded repositories are included in Chapter 3.

The accumulated data are a vital research resource in itself. With continued advancements in high-throughput methods, the sheer volume of data collected has ballooned in recent years, requiring significant investment in systems to house and manage the data. To advance biomedical science, health, and health care, NIH has focused efforts on developing and deploying databases, disease registries, and other biomedical information systems. Specific examples of NIH's efforts in data sharing are provided in Chapter 3.

Additionally, to comply with Section 403 (a)(4)(C)(ii) of the PHS Act*, which requires the* provision of catalogs of disease registries and other data systems, and for the benefit of the larger research community, Appendix G includes a catalog of biomedical information systems and resources.

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 terminology.* NIH leads the government's efforts to develop standardized vocabularies and terminology, which supports interoperability among biomedical information systems in research and clinical settings. NLM is designated within HHS as the central coordinating body for clinical terminology standards.
- *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 the data needed for research, clinical care (including EHRs), and public health.
- *Biomedical informatics research and training.* NIH is the largest federal funder of biomedical informatics research, with the goal of advancing 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.

Figure 15. Next Generation DNA Sequencing. Credit: Darryl Leja, NHGRI

The development, deployment, and utilization of biomedical information resources are essential elements in the management of large amounts of data for research, clinical care, and public health. Increasingly, such 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 targeted small-molecule anticancer agents. New analytical tools

enable researchers to harness large datasets, helping them to address increasingly complex questions, such as how the expression patterns of multiple genes are associated with a particular trait or response. These tools are most effective when databases are interoperable and capable of communicating with one another, and when they make use of similar software applications. At the same time, NIH remains keenly aware of the importance of, and challenges associated with preserving, protecting, and ensuring the validity and security of information stored in biomedical databases.

Because technology allows us to harness the power of the internet, we now have unprecedented access to the health care information in patient files, as well as to raw research data from clinical trials. Shared virtual libraries provide access for health science researchers to data and images from hundreds of studies in various fields. Devising and maintaining the infrastructure to support a seamless end-user environment that encompasses these resources requires the collaboration of a host of professionals in computer science, medicine, information science, records management, and other related fields.

Due to the growing importance of data and its management in biomedical science, clinical care, and public health, almost 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 publicly accessible data and information resources from NLM, have become indispensable as national and international resources for biomedical research and public health. Several NIH-wide activities, including the Big Data to Knowledge (BD2K) initiative,[285] feature the development of significant biomedical information resources, including the tools, infrastructure, and associated research that is required to make the various databases and registries more valuable.

As biomedical research becomes more data intensive, the challenges increase for researchers in releasing, locating, managing, analyzing, and interacting with the 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 to support new methods of managing and analyzing complex and large datasets.

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

Figure 16. Genomic data sharing. Darryl Leja, NHGRI

Technology Development

Technology is moving at an unprecedented pace. Yet new technologies are still needed. We need new, dedicated technologies to help develop a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation, and to help develop a more precise knowledge of the combined effects of environmental exposures, individual susceptibility, and molecular events at the onset of disease. We also need new tech to capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology. Widespread access to such tools will be essential for moving these fields forward.

NIH supports the development of technology through several complementary approaches, including:

- Research project grants that are directed at the development of a particular technology, where some of the projects may take only a few years, and others may continue over a decade or more.
- Bioengineering research partnerships that bring together multiple disciplines in the physical and life sciences—engineering, cell biology, physics, and neuroscience—to develop solutions to specific biomedical questions and understanding of diseases.
- Specialized centers that represent a critical mass of expertise and technology, in which there is multidisciplinary development of complex, often unique technologies, typically in the context of challenging research problems that cannot be approached with existing tools.
- Small business grants through the SBIR and STTR programs for highly innovative projects that may bring technological advances into the marketplace that offer opportunity for the broadest possible availability and impact. These programs allow NIH to leverage unique private-sector resources and perspectives available to complement the work done at universities and the NIH IRP.

- High-risk, innovative projects that may have little preliminary indication of likely success but that could have a 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 fostering 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 sharp 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 2019, 2020, and 2021.

Chapter 3 NIH Research Activities in FY 2019, 2020, and 2021

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 selected NIH research activities from the FY 2019, 2020, and 2021 reporting period. Many of the topics addressed are categories specified in the *PHS Act* (see Appendix A) and are grouped together in one chapter to address the intent of the statute, in terms of presenting information on diseases, disorders, and adverse health conditions in a standardized format.

Cancer

Cancer describes a group of diseases characterized by the common hallmarks of uncontrolled cellular growth and spread of abnormal cells through the body. This uncontrolled cellular growth can lead to benign tumors, which are unable to spread to distant sites in the body, or malignant tumors, which are able to invade normal tissues and spread throughout the body. Cancers are further defined and classified by their cell type, tissue, or organ of origin, and more recently, by genetic markers which can guide treatment. In FY 2019–2021, cancer remained the second leading cause of death in the U.S., following heart disease at number one and followed by COVID-19 at number three. NIH is committed to leading the nation's research efforts to improve cancer prevention, detection, diagnosis, treatment, and survivorship.

Cancer has a major impact on society in the U.S. and across the world. In 2020, the mid-year mark for this triennial report, an estimated 1,806,590 new cases of cancer were diagnosed in the U.S. and 606,520 people died from the disease.[286] The cancers with the highest numbers of cases, starting with the most common, are breast cancer, lung cancer, prostate cancer, colorectal cancer (CRC), melanoma of the skin, bladder cancer, non-Hodgkin lymphoma, kidney cancer, endometrial cancer, leukemia, pancreatic cancer, thyroid cancer, and liver cancer. Estimated national expenditures for cancer care in the U.S. in 2018 were $150.8 billion. In future years, costs are likely to increase as the population ages and more people develop and live with cancer. For example, as of January 2019, there were an estimated 16.9 million cancer survivors in the U.S. The number of cancer survivors is projected to increase to 22.2 million by 2030. Costs are also likely to increase as new, and often more expensive, treatments are adopted as standards of care.

Summary of NIH Activities

NCI leads the agency's cancer research efforts; however, many other NIH ICs conduct and support cancer related research, including the CC, NCATS, NHGRI, NHLBI, NIAID, NIAMS, NIBIB, NICHD, NIDDK, NIEHS, NIGMS, NLM, and the NIH Common Fund. NIH supports research on the molecular basis of cancer and metastasis, the role of the microbiome and the environment, risk factors, prevention, screening and diagnosis, treatment, and survivorship, as well as the development of critical cancer research infrastructure and collaborations that enable coordination across the Nation and throughout the world. Total NIH funding for cancer was $6,520 million in FY 2019, $7,035 million in FY 2020, and $7,362 million

[286] https://www.cancer.gov/about-cancer/understanding/statistics

in FY 2021.[287] As the largest public funder of biomedical research in the world, NIH plays a major role in the progress made by the cancer community, but the more we know, the more questions we have in our work to reduce the burden of cancer for patients, families, and society. Continued efforts need to span the research continuum, from studies of basic biology to examination of cancer rates across the population. NIH support of this broad research agenda can be seen in key initiatives from FY 2019–2021 described throughout this chapter, and as outlined in the *Cancer Trends Progress Report*—which marked 20 years in 2021—and the *Annual Report to the Nation on the Status of Cancer*. In 2019-2021, the *Cancer Trends Progress Report* chapter on prevention was expanded to include measures on the effects of e-cigarettes on youth tobacco use and of genetic testing on CRC, as well as updates to reflect Healthy People 2030 Goals.[288] In the *Annual Report to the Nation on the Status of Cancer* during 2019-2021, researchers found continued declines in cancer mortality rates for men and women, and that overall cancer death rates decreased in every racial and ethnic group during 2013–2017.[289] The reports feature a special section each year, which in 2019-2021 covered cancer trends among adults aged 20-49, progress toward Healthy People 2020 Goals in lung, prostate, female breast, and CRC, and the cost of cancer care in the U.S.

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 (PDAC) and small cell lung cancer research:

- Information on FY 2019, 2020, and 2021 grants funded
- Assessment of progress in these research fields
- Update on activities in these research fields

Expanding Our Understanding of Cancer Biology

Basic and translational research on the cellular, molecular, genetic, biochemical, and immunological mechanisms affecting the development and treatment of cancers is necessary to expand our understanding of this group of diseases. Models of disease are essential to researchers' ability to investigate what biological pathways and mechanisms are relevant to disease progression and vulnerable to manipulation. For example, using a new genetic mouse model of lung squamous cell carcinoma (LSCC), a common type of lung cancer, researchers demonstrated for the first time that a single mutation is sufficient to induce this type of lung cancer.[290,291] According to the authors, this animal model will help scientists discover additional regulators of LSCC development.

Some types of cancer, such as melanoma, are impervious to development of models that look like human disease. Fortunately, researchers developed a new mouse model of melanoma—the deadliest form of

[287] https://report.nih.gov/funding/categorical-spending#/
[288] *Cancer Trends Progress Report.* National Cancer Institute, NIH, HHS, Bethesda, MD, March 2022, https://progressreport.cancer.gov.
[289] Islami F, et al. *J Natl Cancer Inst*. 2021 Jul 8;113(12):1648–69. PMID: 34240195.
[290] https://factor.niehs.nih.gov/2019/6/papers/lung-cancer/index.htm
[291] Liu J, et al. *Nat Commun*. 2019 May 14;10(1):2148. PMID: 31089135.

skin cancer—that reflects human disease.[292] This model has improved the understanding of the biology of melanoma and provided ideas on how to counter it. Looking to the future, this advanced melanoma model will be used to dissect the molecular mechanisms regulating each step of melanoma development and test new therapeutic approaches and assess their potential risks.

Genetics, Cell Biology, and -Omics

Cancer is primarily a genetic disease that starts when a single cell acquires a series of mutations that transform a once-normal cell into a cancerous cell that divides uncontrollably and may eventually spread throughout the body. These mutations are patient-specific and affect individual responses to treatment. NLM researchers developed a computational approach that can be used to predict patient-specific drug response and infer potential drug combinations.[293]

There are two general types of gene mutations that lead to cancer. An oncogene is a mutated gene that has the potential to cause cancer; when not mutated, these genes play a role in normal cell growth and division. Cancer can arise when oncogenes cause the cell to divide and multiply uncontrollably. Some oncogenes work like an accelerator pedal in a car, pushing a cell to divide again and again. Others—known as tumor suppressor genes—work like a faulty brake in a car parked on a hill, also causing the cell to divide unchecked. This may similarly contribute to the development of cancer.

PTEN (phosphatase and tensin homolog) is a tumor suppressor gene that is frequently inactivated in many cancer types. The quest to reactivate *PTEN* has been long and unproductive. Recently, however, researchers found a protein present in many types of cancer, such as liver, breast, and prostate, that suppresses *PTEN*.[294] Deleting this suppressor in mouse models reactivated *PTEN* and inhibited tumor formation. Moreover, researchers discovered a molecule present in cruciferous vegetables that potently inhibits the suppressor, thus activating *PTEN*. These results point towards a long-sought therapeutic strategy to reactivate this tumor suppressor function in many cancer types.

"Omic" technologies capture a holistic view of the molecules that make up a cell, tissue, or organism. Cancer research has capitalized on advances in -omics technologies to expand our understanding of genetics and cellular biology in cancer. This includes genomics, transcriptomics, metabolomics, proteomics, and metagenomics.

Transposable elements are important drivers of tumor growth, yet they are difficult to detect with typical genome sequencing methods due to their ability to move around in the genome. Researchers used a more powerful sequencing technique to provide the first comprehensive look at the role transposable elements play in activating cancer genes in 15 types of cancer.[295,296] The researchers reported that transposable elements switch on cancer-related genes that are usually silent and keep them switched on, which

---

[292] Sun Q, et al. *Nat Commun*. 2019 Nov 4;10(1):5023. PMID: 31685822.
[293] Kim, Y, et al. iScience. 2020 Oct 23; 23(10): 101619. PMID: 33089107.
[294] Lee YR, et al. Science. 2019 May 17;364(6441):eaau0159. PMID: 31097636.
[295] https://factor.niehs.nih.gov/2019/6/papers/dert/index.htm#a1
[296] Jang HS, et al. *Nat Genet*. 2019 Apr;51(4):611-617. Epub 2019 Mar 29. Erratum in: *Nat Genet.* 2019 May;51(5):920. PMID: 30926969.

provides a better understanding of accelerated tumor growth and identifies new targets to study for future cancer therapies.

Alveolar rhabdomyosarcoma (RMS) is a rare cancer in children and adolescents that affects the soft tissues of the torso, arms, or legs, and is associated with a poor prognosis. This cancer is often caused by a specific protein-protein interaction, which changes how DNA in a cell function. NIH researchers used a large, systematic screening approach to determine the specific epigenetic regulators involved in establishment of alveolar RMS.[297] Of the implicated epigenetic regulators, there is already an inhibitor being tested in clinical trials.[298] The insights from this research may help to interpret patient response results of ongoing clinical trials, as well as to develop biomarkers.

The Cancer Genome Atlas (TCGA) is a pivotal cancer genomics program supported by NCI and NHGRI. Since its inception in 2006, TCGA has sequenced and molecularly characterized thousands of primary cancer samples and generated 2.5 petabytes (where 1 petabyte equates to 500 billion pages of standard printed text!) of genomic, epigenomic, transcriptomic, and proteomic data.[299] Recently, TCGA staff, in collaboration with NIH-supported researchers, published a landmark study describing a novel DNA sequencing method on 410 tumor samples spanning 23 cancer types that can help to distinguish different subtypes of cancer, identify mutations that may affect patient survival, describe gene-regulatory interactions underlying cancer immune evasion, and reveal genetic risk loci of cancer predisposition.[300] This work expands scientists' understanding of non-coding regions of the human genome, which will help to better diagnose and treat cancer patients.

Another recent study using TCGA data showed that *DUX4* (double homeobox, 4), which is important for early embryo development but when re-expressed in somatic tissues causes a type of muscular dystrophy, is also highly expressed in cancers from 26 distinct tissue types.[301] Researchers found that the aberrant re-expression of *DUX4* in tumors led to the suppression of anti-tumor immune responses, suggesting that *DUX4* expression in tumors may be a clinically relevant biomarker for response to immune checkpoint blockade.

RNA and proteins also interact to regulate protein activity. For example, *p53* is the most frequently mutated gene in human cancers. Normally, *p53* is a tumor suppressor gene, meaning that its activity stops the formation of tumors; however, when it is mutated, it can instead drive the formation of tumors. Recent studies on CRC suggest that RNA-binding protein, ZMAT3, is important in mediating the tumor-suppressive effects of *p53*.[302]

Understanding how genes affect protein activity and lead to cancer is essential for expanding our understanding of cancer and finding therapeutic targets. Researchers showed that translational

[297] Gryder BE, et al. *Nat Commun.* 2019 Jul 8;10(1):3004. PMID: 31285436.
[298] https://clinicaltrials.gov/ct2/show/NCT02780804
[299] https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga
[300] Corces MR, et al. *Science* 2018 Oct 26;362(6413):eaav1898. PMID: 30361341.
[301] Chew GL, et al. *Dev Cell* 2019 Sep 9;50(5):658-671.e7.PMID: 31327741.
[302] Muys BR, et al. *Genes Dev* 2021 Jan 1;35(1-2):102-116. PMID: 33334821.

reprogramming, which controls the level of genes expressed by a cell at a given time, plays a role in the survival of cancer cells that are deprived of the amino acid asparagine.[303] This amino acid is essential for protein synthesis and cell growth. When researchers used a drug to deprive tumors of asparagine, they found that cancer cells produced this amino acid themselves by turning on a stress response pathway. Further, blocking this stress response pathway with a second drug in mouse tumor models inhibited tumor growth. Based on these preclinical findings, this approach could be a promising cancer treatment.

Cachexia, a significant loss of skeletal muscle and body fat that cannot be halted through nutritional intervention and/or exercise, is a major factor for patients with cancer. Researchers determined that muscle wasting in a mouse model of ovarian cancer is driven not by protein breakdown, but by a decrease in protein production.[304] Specifically, they found reduced production of specific subunits of the ribosome, which is essential for protein production. Another group of researchers demonstrated in multiple mouse models of cancer with cachexia that a protein responsible for stabilizing muscle cell membranes was downregulated, leading to fragile muscle fibers.[305] Complementary studies in patients with PDAC also showed that this protein was decreased in the muscles of patients with cachexia. Understanding the causes of cachexia may uncover new therapeutic targets or direct treatment for the nearly 80 percent of people with cancer affected by it.

NIH-supported researchers developed a gene expression atlas that captures the cellular makeup of the mammary gland across life stages, providing clues on how breast cancer originates.[306] The female breast is made up of different cell types and undergoes reorganization during development, pregnancy, and menopause, increasing breast cancer risk. To build the atlas, the researchers used single cell RNA sequencing data, which assesses gene and protein expression of an individual cell. They integrated data from 50,000 mouse mammary cells, covering eight life stages, and 24,000 adult human mammary cells, using this data to compare genetic profiles for each cell type with known cancer-related genes to infer breast cancer cells of origin.

Humans are composed of populations of cells that are consolidated into tissues and organs and work together to make the proteins and other necessary biomolecules. However, each of those types of cells has a specific role to play —for example, only B cells will make antibodies, so if a scientist finds a cell that is making antibodies, they can conclude that this cell is a B cell. Researchers funded by the NIH Common Fund Human BioMolecular Atlas Program (HuBMAP) are generating molecular profiles of proteins that can identify certain kinds of cells, and then use those profiles to predict where the cells are in relationship to each other in healthy tissue and tumor samples.[307] HuBMAP researchers and colleagues developed a computational method, single-cell metabolic regulome profiling (scMEP), to identify the type of cell in a sample and what metabolic processes that cell is performing at a specific moment.[308] This knowledge will

[303] Pathria G, et al. *Nat Cell Biol* 2019 Dec;21(12):1590-1603. PMID: 31740775.
[304] Kim HG, et al. *FASEB J* 2021 Feb;35(2):e21335. PMID: 33527503.
[305] Judge SM, et al. *Cancer Res* 2020 May 1;80(9):1861-1874. PMID: 32132110.
[306] https://factor.niehs.nih.gov/2021/8/papers/dert/index.htm#a3
[307] https://commonfund.nih.gov/hubmap/highlights
[308] Hartmann FJ, et al. *Nat Biotechnol* 2021 Feb;39(2):186-197. PMID: 32868913.

help researchers better predict how patients might respond to immunotherapy, or find new biomarkers to enable earlier diagnoses of disease or therapeutic targets.

Microbiome and Cancer

Many people are now aware of their microbiome—the community of microbes that live throughout and on their body. However, most may not be aware that this microbiome includes bacteria, viruses, and fungi. When one thinks of fungus, one probably thinks of yeast and mushrooms. There are tens of thousands of organisms that are classified as fungi, and fungi can affect people in both positive and negative ways. Certain fungi are the source of antibiotics like penicillin; however, other types of fungi can also cause infections in the body. For more information, see the Microbiome section in this Chapter.

Researchers found that certain fungi travel from the gut into the pancreas and can promote tumor initiation in the organ.[309] In mice and humans with pancreatic cancer, these fungi increased 3,000-fold compared to those in normal tissue. The fungal composition of pancreatic cancer tissues was distinct from both gut and normal pancreatic tissues. An antifungal drug inhibited tumor growth in preclinical models, and repopulation of the main fungal type in antifungal-treated mice caused pancreatic tumor growth. This is the first study to provide some evidence that the fungal component of the pancreatic microbiome may promote changes that lead to pancreatic cancer development and progression, suggesting the possibility of using antifungal drugs to treat or prevent pancreatic cancer.[310] Further research will be needed before antifungal agents are added to pancreatic cancer treatment regimens due to their serious side effects.

Metastasis

Metastasis is the spread and growth of tumor cells away from the primary site of cancer. For example, patients undergoing treatment for ovarian cancer are checked for tumor cells that may have spread to surrounding tissues. Current technologies can miss very small metastatic areas; however, a new laser microscopy technique is able to identify these regions with greater accuracy.[311] This unique microscopy technique functions without any sort of chemical labeling or processing of the tissue, enabling it to be used in real-time during surgery.[312] The ultimate aim of using this technology during surgery—to detect and remove routinely missed metastases—may significantly improve surgical outcomes for patients being treated for ovarian cancer, and may be applicable to other types of cancer.

Most cancer researchers have assumed that the spread, or metastasis, of tumors typically occurs later in the disease process. The general concept has been that as tumors grow and cancer cells accumulate additional genetic changes, or mutations, some cells acquire the ability to move from the primary tumor into the bloodstream or lymphatic system, to migrate to a distant location in the body, and to grow into tumors in the new location. However, studies in FY 2019–2021 by NIH and NIH-supported scientists have challenged the paradigm of when tumor cell metastasize to distant sites.

---

[309] Aykut B, et al. *Nature* 2019 Oct;574(7777):264-267. PMID: 31578522.
[310] https://moffitt.org/endeavor/archive/can-fungi-drive-pancreatic-cancer/
[311] https://www.nibib.nih.gov/news-events/newsroom/label-free-microscope-detects-ovarian-metastatic-cancer
[312] Pouli D, et al. *Biomed Opt Express* 2019 Aug 6;10(9):4479-4488. PMID: 31565503.

CRC is a commonly diagnosed cancer that often spreads to the liver and the brain. The timing of colorectal metastases is not well understood. Using genomic and phylogenetic analyses to study primary and metastatic colorectal tumors, NIH-supported researchers discovered that in 80 percent of patients with colorectal metastases, the spread of metastatic cells occurred early, when the primary tumor was too small to be clinically detectable.[313] This result is at odds with prevailing dogma that metastasis usually occurs at later stages of the disease. While treatments that specifically target metastatic tumors do not yet exist, these findings may provide clues on how to target and eliminate such cells in the bloodstream.[314]

Another study may provide important insights into why some melanomas are more likely to spread than others.[315] The researchers showed that melanoma cells are more likely to metastasize if they produce high levels of the transporter protein MCT1 (monocarboxylate transporter 1).[316] This protein enhances the cells' ability to take up a nutrient called lactate. Lactate increases the cells' ability to manage oxidative stress, which helps prevent DNA damage and other types of cellular damage. This altered metabolism helps melanoma cells survive as they spread throughout the body to form secondary tumors in other organs. Researchers hope that these studies will provide new insights into ways of blocking the early stages of metastasis.

For some breast cancer patients that have been treated with chemotherapy, distant metastases can appear years or even decades later. Studies have shown that tumor cells can leave the primary tumor site and exist in a dormant state elsewhere in the body, only to reawaken years later and start to grow into a metastasis.[317] It has been hypothesized that the dormant state is what protects the tumor cells from being killed by chemotherapy. Recent studies from NIH-supported researchers suggest that the bone marrow microenvironment—where these dormant tumor cells hide—is what protects them from the effects of chemotherapy rather than the dormant state.[318] Inhibiting interactions between the dormant tumor cells and the bone marrow microenvironment prevented bone metastasis in experimental models of breast cancer. While these experiments were performed in cell culture and mouse models, it will take time to develop therapies that would similarly inhibit this protective relationship in human patients. If developed, such therapies could help prevent breast cancer metastases.

Cancer therapy can be a necessary double-edged sword, as surgery and chemotherapy to remove and kill the tumor can also turn on the body's natural responses to injury, which include activating inflammatory and immunosuppressive pathways that allow for tumor escape and recurrence. Researchers hypothesized that these events could be altered by either blocking the inflammatory cascade and/or by accelerating the resolution of inflammation. Preoperative, but not postoperative, administration of the nonsteroidal anti-inflammatory drug ketorolac and/or resolvins—a family of molecules that activate the white blood cells responsible for resolving inflammation—eliminated micrometastases in multiple tumor-resection

[313] Hu Z, et al. *Nat Genet* 2019 Jul;51(7):1113-1122. PMID: 31209394.
[314] https://www.cancer.gov/news-events/cancer-currents-blog/2019/early-metastasis-colorectal-cancer
[315] https://www.cancer.gov/news-events/cancer-currents-blog/2020/melanoma-metastasis-metabolism-mct1
[316] Tasdogan A, et al. *Nature* 2020 Jan;577(7788):115-120. PMID: 31853067.
[317] https://www.cancer.gov/news-events/cancer-currents-blog/2019/breast-cancer-chemotherapy-sensitizing-dormant-cells
[318] Carlson P, et al. *Nat Cell Biol* 2019 Feb;21(2):238-250. PMID: 30664790.

models, resulting in long-term survival.[319] Giving the treatments together had an even stronger anti-tumor effect. This work could prove to be beneficial for patients with cancer undergoing surgery, as well as the 30 percent of patients without diagnosed cancer undergoing surgery who harbor microscopic clusters of cancer cells.

Environmental Health and Cancer

Understanding both the toxicity of chemicals and how different compounds can function as carcinogens are important areas of research on cancer and many other diseases. As exposures leading to toxicity happen over time in real world settings, traditional tests for chemical toxicity and carcinogenicity require at least two years of experiments. To determine if long-term experiments were always necessary, NIH researchers developed a new test to measure chemical toxicity in the liver and kidneys that only takes five days.[320] The tests were shown to produce similar results as those observed in rats in long-term experiments, suggesting that short-term experiments can also provide a rapid and effective estimate of toxicological potency.[321]

The health hazards associated with cigarette smoking are well known. These include lung disease, cardiovascular disease, and cancer. Electronic cigarettes (e-cigarettes) use battery power to heat a nicotine-containing solution into an inhalable vapor. The inhaled vapor may contain nicotine (the addictive drug in tobacco), flavorings, and toxins—including ones that cause cancer. Mice exposed to e-cigarette smoke were more likely to develop lung adenocarcinomas, a type of lung cancer, and had higher levels of bladder urothelial hyperplasia, an abnormal increase in epithelial cells that can precede development of bladder tumors.[322]

Developing Better Screening and Interventions to Prevent Cancer

Checking for cancer (or for abnormal cells that may become cancer) in people who have no symptoms is called screening. Several screening tests have been shown to detect cells that could become cancer or are early-stage cancer and to reduce the chance of death from that cancer.

Developing screening tests that detect multiple cancers will allow for earlier intervention and improved patient outcomes. Investigators from the Early Detection Research Network participated in the development and testing of CancerSEEK, a test that simultaneously determines the levels of eight proteins and the presence of 16 cancer gene mutations in circulating DNA. The test is aimed at screening for eight common cancer types that account for more than 60 percent of cancer deaths in the U.S., five of which currently have no screening test.[323]

In FY 2021, two studies made great strides in predicting cancer development and treatment response in two childhood cancers. Patients with the inherited condition neurofibromatosis type 1 (NF1) are usually

---

[319] Panigrahy D, et al. *J Clin Invest* 2019 Jun 17;129(7):2964-2979. PMID: 31205032.
[320] Gwinn WM, et al. *Toxicol Sci* 2020 Aug 1;176(2):343-354. PMID: 32492150.
[321] https://factor.niehs.nih.gov/2020/8/papers/dir/index.htm#a1
[322] Tang MS, et al. *Proc Natl Acad Sci U S A.* 2019 Oct 22;116(43):21727-21731. Erratum in: *Proc Natl Acad Sci U S A.* 2019 Nov 5;116(45):22884. PMID: 31591243.
[323] https://www.cancer.gov/news-events/cancer-currents-blog/2020/cancerseek-blood-test-detect-early-cancer

diagnosed in childhood and often develop non-cancerous, or benign, tumors that grow along nerves. These tumors can sometimes turn into aggressive cancers, but there has not been a good way to determine whether this transformation to cancer has happened. One study developed a blood test for NF1; current methods to determine the transition to cancer can be difficult and painful and this new blood test can help monitor if and when this transition happens, as well as help predict the patient's response to treatment.[324,325] The second study identified genomic markers that could be used for risk stratification in patients with RMS, the most common soft tissue sarcoma of childhood.[326] This study was the largest-ever international genomic characterization of clinically annotated RMS tumors to date. These results are currently being incorporated into prospective clinical trials and could hopefully lead to routine tumor genetic testing for rare cancers such as RMS.

Each year, more than 500,000 women worldwide are diagnosed with cervical cancer. Almost all of these cases are caused by the human papilloma virus (HPV). Of about 200 known HPV variants, only 13 can transform healthy cells of the cervix into pre-cancerous lesions and eventually into cancer.[327] HPV genotyping is now recommended for primary screening. The traditional test to detect abnormal cervical cells, pre-cancers, and cancer is the Pap test, in which the cervical cells are collected and analyzed by a pathologist. In lower-resource settings, visual inspections are used. All of these methods have limitations. The sensitivity, or ability to identify true positives, of Pap and visual tests is about 70 percent. Likewise, commercial assays for HPV genotyping are slow and expensive. From FY 2019–2021, NIH researchers made advances in all three areas. They developed a computer algorithm based on AI that analyzes cervical images and identifies precancerous changes more accurately than standard tests.[328] This screening tool can be used in low-resource settings. For HPV genotyping, researchers developed TypeSeq, a high-throughput, low-cost HPV test, which is already employed as a gold standard in some regulatory trials.[329] When suspicious cervical lesions are found, a woman is usually referred for a biopsy. Since most lesions can be cleared by the immune system, many biopsies are performed unnecessarily. Researchers developed a dual-stain test that helps to reduce unnecessary biopsies. This test predicts more accurately than a Pap test whether an HPV-positive woman with a suspicious lesion is at high risk to develop cervical precancer.[330] Because this test still requires visual interpretation, which is subjective and costly, researchers developed an AI-based automated testing platform. The resulting test reduces referral to biopsy by one-third.[331] Overall, researchers made significant advances in cervical cancer prevention, some of which have already begun to benefit women.

Cancer rates in people with HIV infection are increasing, including anal cancer caused by HPV.[332] A phase 3 clinical trial conducted by the AIDS Malignancy Consortium was designed to determine if routine

[324] https://www.cancer.gov/news-events/press-releases/2021/neurofibromatosis-cancer-blood-test
[325] Szymanski JJ, et al. *PLoS Med* 2021 Aug 31;18(8):e1003734. PMID: 34464388.
[326] Shern JF, et al. *J Clin Oncol* 2021 Sep 10;39(26):2859-2871. PMID: 34166060.
[327] https://www.cdc.gov/cancer/hpv/basic_info/index.htm
[328] Hu L, et al. *J Natl Cancer Inst* 2019 Sep 1;111(9):923-932. PMID: 30629194.
[329] Wagner S, et al. *J Infect Dis* 2019 Oct 8;220(10):1609-1619. PMID: 31536132.
[330] Clarke MA, et al. *JAMA Oncol* 2019 Feb 1;5(2):181-186. PMID: 30325982.
[331] Wentzensen N, et al. *J Natl Cancer Inst* 2021 Jan 4;113(1):72-79. PMID: 32584382.
[332] Clifford GM, et al. *Int J Cancer* 2021 Jan 1;148(1):38-47. PMID: 32621759.

screening and removal of precancerous cells helped to decrease the rate of cancer in this population.[333,334] The study demonstrated that removing the precancerous cells significantly reduced the risk of progression to anal cancer among people with HIV.[335] The trial was halted early because of its high success rates, indicating this approach could become the standard of care for people with HIV or others at high risk for anal cancer.

Esophageal adenocarcinoma is a cancer that usually forms in the lower part of the esophagus. Barrett's esophagus (BE) is a known precursor state of esophageal adenocarcinoma. BE can be detected by endoscopy, which is highly invasive and costly for population screening. Researchers developed a swallowable pill-sized device called EsoCheck that can be used in an outpatient setting to collect cells of the esophagus within five minutes. Clinical trials found the EsoCheck procedure to be well tolerated and the device has secured FDA clearance.[336] Collected cells are tested to confirm that they are from the esophagus, the sensitivity and specificity of which are both about 90 percent. EsoCheck is a cost-efficient way to screen at-risk populations for BE and esophageal cancer.

Scientists have developed a new test that can help identify people who are likely to develop hepatocellular carcinoma (HCC), the most common form of liver cancer.[337] The approach uses a simple blood test to check for the patient's previous exposure to certain viruses. Certain factors increase a person's chances of developing HCC, such as infection with hepatitis B or hepatitis C virus or cirrhosis of the liver. People who have risk factors are recommended to get screened for HCC every six months. Although screening can lead to earlier detection, most patients are diagnosed when the cancer is advanced and often incurable. However, when HCC is detected early, patients have a much better chance of being cured. NIH investigators identified a viral signature, based on the presence of specific viral antibodies in an individual's blood, that can predict the development of HCC.[338] This viral signature was shown to be highly predictive of HCC in at-risk patients even ten years before clinical diagnosis, increasing the chances of early detection and successful treatment.

The PREVENT Cancer Preclinical Drug Development Program (PREVENT) supports preclinical development of innovative interventions and biomarkers for cancer prevention. Recent PREVENT studies looked at the efficacy of cancer vaccine candidates targeting commonly recurring mutated proteins associated with cancer development in Lynch syndrome (LS), a genetic disorder that leads to an increased risk of certain cancers including CRC. Using a mouse model of LS, researchers found these cancer vaccine candidates can promote an immune response and lead to a significant reduction in tumor load plus prolonged survival, and when combined daily with a low dose non-steroidal anti-inflammatory drug (naproxen), these results

[333] https://anchorstudy.org/
[334] https://clinicaltrials.gov/ct2/show/NCT02135419
[335] https://cancer.ucsf.edu/news/2021/10/08/treating-anal-cancer-precursor-lesions-reduces-cancer-risk-for-people-with-hiv
[336] https://prevention.cancer.gov/news-and-events/blog/new-technology-gives-patients
[337] https://www.cancer.gov/news-events/press-releases/2020/liver-cancer-screening-test
[338] Liu J, et al. *Cell* 2020 Jul 23;182(2):317-328.e10. PMID: 32526205.

were even more pronounced.[339] These preclinical findings support the feasibility of this clinical vaccination approach as a cancer prevention strategy in patients with LS.

Developing and Improving Interventions to Treat Cancer

Immunotherapy

The immune system's natural ability to detect and destroy abnormal cells prevents many cancers from ever developing, just like it protects from infections. However, cancer cells can co-opt the body's immune defenses to evade detection and boost cancer growth. In the relatively new field of cancer immunotherapy, scientists are killing cancer cells by enlisting a person's own immune system to control and, in some cases, even cure their cancer. Decades of NIH research has led to several types of cancer immunotherapy drugs. These include mimics of natural immune-system molecules, such as anti-cancer antibodies, supercharged immune cells, or treatment vaccines that "teach" an individual's immune system to attack tumors. NIH researchers are investigating the factors that affect whether a tumor will respond to immunotherapy, providing clues for matching tumors to drugs.

A team of researchers from NIH and the College of Agriculture, Environment and Nutrition Sciences at Tuskegee identified a potential new therapeutic strategy that employs the immune system against cancer.[340] In the study, researchers tapped into an ancient part of immune system defenses used by organisms to fend off bacteria, viruses, and other foreign invaders to reprogram and turn on tumor-associated macrophages (a type of immune cell) to begin killing–literally eating–cancer cells.[341]

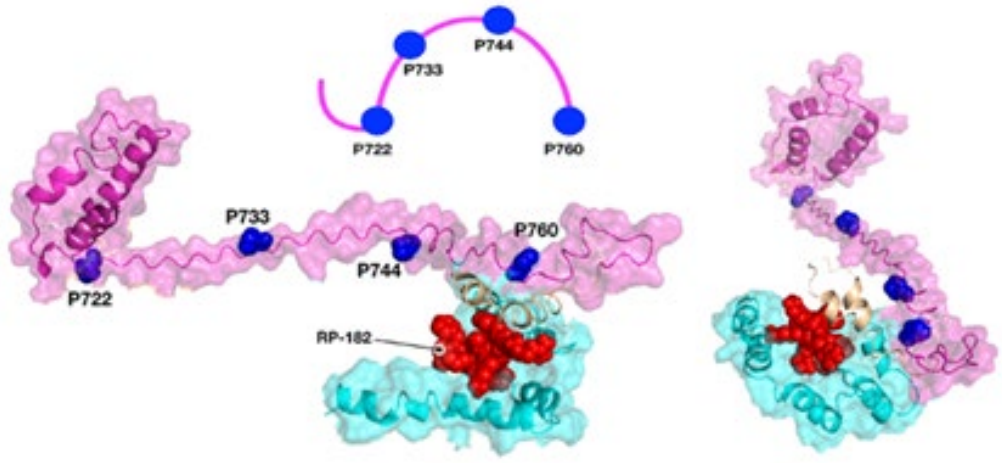


Figure 17: A model shows how the small RP-182 protein, or peptide, (shown in red) is nestled inside the CD206 receptor in two specific locations (shown in magenta and cyan). This alters the receptor's shape and activates the receptor. Credit: Jaynes et al., Sci. Transl. Med. PMID: 32051227

[339] Gebert J, et al. *Gastroenterology* 2021 Oct;161(4):1288-1302.e13. Erratum in: *Gastroenterology* 2021 Dec;161(6):2070. PMID: 34224739.
[340] https://www.tuskegee.edu/news/tuskegee-nih-researchers-develop-potential-method-of-reprogramming-immune-cells-to-fight-cancer-other-diseases
[341] Jaynes JM, et al. *Sci Transl Med* 2020 Feb 12;12(530):eaax6337. PMID: 32051227.

Chimeric antigen receptor (CAR) T cell therapy has been successful for some hematological cancers with few treatment options, including leukemias and lymphoma; however, challenges exist with optimal CAR T cell therapy for solid tumors. These include ensuring specificity to tumor cells and avoiding tumor escape, or adaptations that allow tumor cells to survive due to antigen loss preventing an immune response. To overcome these barriers, researchers developed synthetic Notch (synNotch)-CAR T cells that target solid tumors with more specific and persistent antitumor activity.[342,343] SynNotch-CAR T cells were better at controlling tumors than traditional CAR T cells in preclinical trials and did not result in toxicity in multiple solid tumors. These results suggest that synNotch-CAR T cells may be an effective immunotherapy approach.

Multiple myeloma remains an incurable blood cancer of plasma cells, the white blood cells that make antibodies. Despite new treatments, such as monoclonal antibodies and proteasome inhibitors, patients invariably relapse, underscoring a dire need for new types of therapy. Researchers conducted a phase 1 clinical trial with CAR T cell therapy, infusing patients with T cells that can recognize and target plasma cells.[344] Disease burden was reduced by half or more in eighty five percent of patients, but the majority of patients experienced significant side effects, a common concern for patients receiving immunotherapies.

Immune checkpoints are a normal part of the immune system that prevent an immune response from being so strong that it destroys healthy cells in the body. Immunotherapy drugs called immune checkpoint inhibitors (ICI) work by blocking checkpoint proteins from binding with their partner proteins.[345] ICI can cause a variety of immune-related adverse events, including inflammatory arthritis. Investigators characterized a group of 60 patients with ICI inflammatory arthritis and found a large subgroup of patients with persistent disease up to 24 months after stopping ICI therapy.[346] In addition, they showed that the risk of persistent inflammatory arthritis is associated with several factors including response to ICI therapy, longer ICI treatment, use of combination ICI therapy, and experiencing other types of immune-related adverse events. Furthermore, drugs that reduce the immune response were effective in controlling symptoms of ICI inflammatory arthritis without compromising the tumor response. Collectively, these findings provide a foundation for understanding clinical subgroups, persistence, and risk factors in ICI inflammatory arthritis.

Liver cancer is the second most lethal malignancy worldwide. ICI have been effective in some, but not all patients, most likely because liver tumors are diverse and vary at the cellular level. NIH researchers developed methods to measure cellular diversity in tumors at the transcriptome (mRNA) level from patients treated with ICI and found that higher diversity corresponded to worse patient outcomes.[347]

---

[342] Hyrenius-Wittsten A, et al. *Sci Transl Med* 2021 Apr 28;13(591):eabd8836. PMID: 33910981.
[343] Choe JH, et al. *Sci Transl Med* 2021 Apr 28;13(591):eabe7378. PMID: 33910979.
[344] Raje N, et al. *N Engl J Med*. 2019 May 2;380(18):1726-1737. PMID: 31042825.
[345] https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors#:~:text=Immunotherapy%20drugs%20called%20immune%20checkpoint,checkpoint%20protein%20called%20CTLA%2D4
[346] Braaten TJ, et al. *Ann Rheum Dis*. 2020 Mar;79(3):332-338. PMID: 31540935.
[347] Ma L, et al. *Cancer Cell.* 2019 Oct 14;36(4):418-430.e6. PMID: 31588021.

These results suggest that a transcriptomic diversity score may be useful in predicting outcomes for liver cancer patients treated with ICI. In addition, the study found that the therapeutic efficacy of ICI may be increased by combining them with drugs that blocked blood vessel growth to the tumor.

In an important advancement for precision oncology, researchers have shown how a tumor analysis pipeline can identify which therapies may be particularly beneficial for individual patients.[348] When applied to data from over 30 different targeted and immunotherapy clinical trials, the pipeline was predictive of patient responses to these therapies in about 80 percent of the trials.[349] This pipeline is the first modeling approach able to obtain such predictive accuracies across so many targeted immunotherapy datasets. It offers a promising way to increase the number of patients who could benefit from precision-based treatments in the future and provides a basis for further testing and improvement in transcriptomics-based precision oncology clinical trials.

Combination Therapy

Combination therapy is a treatment regimen that combines two or more therapeutic agents and is a cornerstone of cancer therapy. Combining different types of anti-cancer drugs enhances efficacy compared to a single therapy approach because the drugs can work together to target key pathways.

Researchers have devised a new plan of attack against a group of deadly childhood brain cancers collectively called diffuse midline gliomas. NIH and NIH-supported scientists identified a drug pair using the NCATS Pharmaceutical Collection that worked together to both kill cancer cells and counter the effects of a genetic mutation that causes the diseases.[350] The researchers showed that combining the two drugs was more effective than either drug by itself in killing cancer cells grown in the laboratory and in animal models.[351] Their studies also uncovered a previously unrecognized vulnerability in the cancer cells that scientists may be able to exploit to develop new strategies against this cancer and related diseases.

In April 2020, FDA granted approval for a drug called Selumetinib as a treatment for pediatric patients with NF1, who have symptomatic, inoperable non-cancerous peripheral nerve tumors.[352] The approval was based on the results of a longitudinal natural history study of NF1 and phase 1 and 2 trials conducted at NCI, along with collaborating sites across the country.[353,354] Researchers found that NF1 patients treated with Selumetinib experienced improvements in clinical outcomes such as decreased pain, more strength, and a better quality of life.[355] Selumetinib is the first and only FDA-approved treatment for pediatric patients who have this debilitating, and often disfiguring, rare disease.

---

[348] https://ccr.cancer.gov/news/article/new-tool-predicts-which-treatments-may-work-best-in-cancer-patients
[349] Lee JS, et al. *Cell.* 2021 Apr 29;184(9):2487-2502.e13. PMID: 33857424.
[350] https://ncats.nih.gov/news/releases/2019/childhood-brain-cancer
[351] Lin GL, et al. *Sci Transl Med.* 2019 Nov 20;11(519):eaaw0064. PMID: 31748226.
[352] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selumetinib-neurofibromatosis-type-1-symptomatic-inoperable-plexiform-neurofibromas
[353] Akshintala S, et al. *Neuro Oncol.* 2020 Sep 29;22(9):1368-1378. PMID: 32152628.
[354] https://clinicaltrials.gov/ct2/show/NCT00924196
[355] Gross AM, et al. *N Engl J Med.* 2020 Apr 9;382(15):1430-1442. Erratum in: *N Engl J Med*. 2020 Sep 24;383(13):1290. PMID: 32187457.

There are many types of breast cancer, and the type or subtype of breast cancer often determines the treatment regimen used. For example, estrogen can lead to breast cancer cell growth and hormone therapy that blocks the ability of cells to use estrogen may prevent further cancer growth; it is not known whether this approach is more effective in combination with chemotherapy. A clinical trial for patients with hormone receptor positive and HER2 (human epidermal growth factor receptor 2) negative breast cancer that has spread beyond the primary tumor aimed to assess whether there was a benefit to adding chemotherapy to hormone therapy. Early results found no difference in disease-free survival in post-menopausal women treated with hormone therapy alone versus those treated with chemotherapy and hormone therapy, but premenopausal women who received chemotherapy and hormone therapy had superior disease-free survival compared with those who received hormone therapy alone.[356] It is unknown whether this difference can be attributed to an actual benefit of chemotherapy, or whether this may be due to the ovarian suppression induced by chemotherapy. The trial does indicate that hormone therapy alone is effective for post-menopausal patients with this breast cancer subtype.

Triple negative breast cancer is one of the most challenging types of breast cancer to treat since the commonly targeted receptors are absent. In April 2020, the FDA granted accelerated approval to a new drug (Trodelvy) for the treatment of adult patients with triple-negative breast cancer that has spread to other parts of the body by targeting a receptor that helps the cancer grow and spread.[357] This was followed one year later by regular approval based on findings from a much larger confirmatory clinical trial that showed the drug improved how long patients lived compared with standard chemotherapy treatments.[358] The company that developed the drug used NIH Small Business Innovation Research (SBIR) funding to support the development of the therapy.

BRCA1 (BReast CAncer gene 1) and *BRCA2* (BReast CAncer gene 2) are genes that produce proteins that help repair damaged DNA; they are tumor suppressor genes. People who inherit harmful variants in one of these genes have increased risks of several cancers, most notably breast and ovarian cancer, but also several additional types of cancer. People who have inherited a harmful variant in *BRCA1* and *BRCA2* also tend to develop cancer at younger ages than people who do not have such a variant.

There is a need for new therapies to reduce cancer recurrence in patients with early *BRCA1* or *BRCA2* mutation-associated breast cancers. A phase 3 clinical trial funded in part by NCI assessed the efficacy of giving a drug (olaparib) to women with early-stage breast cancer and a *BRCA1/2* mutation who had completed local treatment and chemotherapy.[359] Results of the trial showed that those given olaparib for 52 weeks after local treatment and chemotherapy had significantly longer disease-free survival (85.9 percent) compared to those given a placebo pill (77.1 percent), and only had limited effects on overall

[356] https://www.cancer.gov/news-events/press-releases/2020/breast-cancer-treament-postmenopausal-women-may-forgo-chemotherapy
[357] https://www.fda.gov/news-events/press-announcements/fda-approves-new-therapy-triple-negative-breast-cancer-has-spread-not-responded-other-treatments
[358] https://www.cancer.gov/news-events/cancer-currents-blog/2021/sacituzumab-govitecan-tnbc-regular-approval
[359] Tutt ANJ, et al. *N Engl J Med*. 2021 Jun 24;384(25):2394-2405. PMID: 34081848.

patient-reported quality of life. This trial also showed the importance of sequencing *BRCA1* and *BRCA2* as biomarkers for treatment selection in early breast cancer.

High-grade serous ovarian cancer (HGSOC) is the most common subtype of epithelial ovarian cancer. In almost all patients, HGSOC cells are under replication stress, meaning that DNA replication is slowed or stalled during cell division. Patients with HGSOC that has come back and is no longer responsive to platinum-based therapy—called recurrent platinum-resistant HGSOC—are often treated with gemcitabine, which induces even more replication stress. In response to this stress, the cancer cells activate the serine/threonine-protein (ATR) kinase protein to help stabilize DNA replication. Researchers exploited this reaction by inhibiting it with berzosertib, an ATR-specific drug. Specifically, they conducted a randomized phase 2 clinical trial comparing a combination of berzosertib and gemcitabine with gemcitabine alone.[360] The drug combination extended progression-free survival, which warrants further investigation in a phase 3 clinical trial and suggests that this drug combination could be effective against other tumor types with high replication stress, such as small cell lung cancer.

Low-grade serous ovarian cancer (LGSOC) is rare and understudied. Although this cancer is usually treated with chemotherapy and/or hormone therapy, the optimal first-line treatment is not known. Seventy percent of patients diagnosed with advanced stage disease relapse and, following relapse, this histologic subtype is relatively chemo-resistant, underscoring the importance of determining the best first-line treatment. Researchers conducted a randomized international phase 2/3 clinical trial in patients with relapsed or persistent LGSOC, comparing physician's choice of standard-of-care, either chemotherapy or hormone therapy, with trametinib.[361] Trametinib increased progression-free survival and objective response rate. Improvements in response duration and overall survival were also observed. These findings indicate that trametinib may become a new standard-of-care treatment option for patients with recurrent LGSOC.

People with the rare inherited disorder von Hippel-Lindau (VHL) disease have an increased risk of developing cancerous and noncancerous tumors in multiple organs, including the kidneys, pancreas, brain, and spine. Doctors typically perform surgery to remove these tumors when they grow to a critical size to prevent cancer from spreading or impacting organ function, but with each successive surgery the risk of complications increases, highlighting a need for systemic therapies. NIH researchers conducted a phase 2 clinical study to investigate the efficacy and safety of belzutifan (Welireg), a drug that inhibits tumor growth-promoting protein complexes, in patients with VHL disease-associated renal cell carcinoma, which 70 percent of patients with VHL disease develop during their lifetime.[362] The outcome of this trial resulted in FDA approval of belzutifan for the treatment of adults with cancers associated with VHL and is

[360] Konstantinopoulos PA, et al. *Lancet Oncol*. 2020 Jul;21(7):957-968. PMID: 32553118.
[361] https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress/A-Randomized-Phase-II-III-Study-to-Assess-the-Efficacy-of-Trametinib-in-Patients-with-Recurrent-or-Progressive-Low-Grade-Serous-Ovarian-or-Peritoneal-Cancer
[362] https://www.cancer.gov/news-events/cancer-currents-blog/2021/fda-belzutifan-vhl-tumors

the first FDA approved drug for the treatment of VHL-associated cancers, reducing the need for surgery and the associated complications.[363]

NIH and NIH-supported researchers have devised a potential treatment against a common type of leukemia that could have implications for many other types of cancer.[364] The new approach takes aim at a way that cancer cells evade the effects of drugs, a process called adaptive resistance. Through multiple studies, the researchers identified a cellular pathway that allows a form of acute myeloid leukemia (AML), a deadly blood and bone marrow cancer, to elude the activity of a promising class of drugs.[365] They then engineered a compound that launches a two-pronged attack against the cancer. In several experiments, the compound blocked a mutated protein that causes AML, and it halted the cancer cells' ability to sidestep the compound's effects. The results could lead to the development of new therapies against AML and cancers that act in similar ways.

Retrospective studies suggested that allogenic hematopoietic cell transplant (alloHCT), a stem cell transplant from a matched donor, is feasible in HIV positive patients with hematologic malignancies (blood cell cancers). In the present study, researchers conducted a phase 2 multi-center clinical trial to prospectively evaluate the safety and effectiveness of alloHCT for HIV positive patients with hematologic malignancies.[366] In alloHCT, a donor's hematopoietic cells are transferred to the recipient's bone marrow. Hematopoietic stem cells reside in the bone marrow and give rise to different kinds of blood cells. In the present study, two-thirds of the patients achieved successful engraftment of donor cells in the recipient and researchers did not observe an increased risk of disease relapse in the HIV positive patients. The safety outcomes indicate that HIV infection should not be considered a contraindication to alloHCT in patients, in whom HIV can be suppressed with antiretroviral therapy. This study also suggests that HIV patients should not be excluded from clinical trials aimed at reducing relapse or progression of malignant disease.

Kaposi sarcoma (KS) is a cancer of the cells lining blood and lymph vessels that often occurs in immunocompromised individuals, including those with HIV infection or AIDS. KS lacks oral therapies or treatments that can be delivered in resource-limited settings. NIH scientists conducted a clinical trial that showed an oral immune modulating drug (pomalidomide) is active against KS and well tolerated regardless of HIV status. This trial led to the FDA granting accelerated approval of this drug for use in KS in May 2020.[367] This is the first new drug approved for KS in over a decade and trials are ongoing to study its efficacy against KS in Africa and in combination with a chemotherapy drug.

---

[363] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease

[364] https://www.nih.gov/news-events/news-releases/nih-cincinnati-childrens-scientists-develop-potential-strategy-against-leukemia-drug-resistance

[365] Melgar K, et al. *Sci Transl Med.* 2019 Sep 4;11(508):eaaw8828. PMID: 31484791.

[366] Ambinder RF, et al. *Biol Blood Marrow Transplant*. 2019 Nov;25(11):2160-2166. PMID: 31279752.

[367] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pomalidomide-kaposi-sarcoma

Conducting Public Health Research Studies to Better Understand Cancer

Epidemiology

Epidemiology is a cornerstone of cancer prevention and care, as this research field describes the distribution of diseases like cancer and discovery of risk factors for those diseases.

The Connect for Cancer Prevention Study is a new prospective cohort of 200,000 diverse adults in the U.S. designed to further investigate the causes of cancer and learn how to better prevent it.[368] The new cohort will capitalize on research innovations to advance the fields of cancer epidemiology and prevention, including new technologies for exposure assessment (e.g., tracking and sensors to measure behavior and environment) and large-scale analyses of the genome, epigenome, transcriptome, proteome, metabolome, and microbiome of tumors and precursor lesions. Recruitment through the partnering health care institutions will occur between 2021 and 2026.

The Surveillance, Epidemiology, and End Results (SEER) Program provides information on cancer statistics to reduce the cancer burden among the U.S. population.[369] SEER collects and publishes cancer incidence and survival data from U.S. population-based cancer registries covering approximately 50 percent of the U.S. population (up from approximately 34.6 percent in FY 2020). These registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status (survival). In FY 2019, the SEER Program developed the *Did You Know?* video series to highlight key topics and trends in cancer statistics to build awareness across broad audiences. The video library includes 25 three- to four-minute informational videos on various cancer topics, which can be embedded on any website or presentation or shared by email.[370] In FY 2020 and FY 2021, the SEER Program also worked with the cancer surveillance community and other partners on a coordinated approach to develop a database of all COVID-19-related activities, such as surveys and data collection, that could have an impact on cancer surveillance research.[371]

Although advances in cancer treatment have improved survival for patients, survivors may be at increased risk of developing a subsequent treatment-related cancer. Using SEER Program registry data and treatment information from the SEER-Medicare database, NIH researchers followed patients who were diagnosed with a primary tumor from 2000 to 2014.[372] The researchers published their study in 2020 demonstrating that patients treated with chemotherapy for almost all solid tumor types (22 of 23) experienced an increased risk of therapy-related myelodysplastic syndrome/acute myeloid leukemia (tMDS/AML), which is a rare but often fatal blood cancer. These findings expand the groups of cancer survivors at risk for tMDS/AML following treatment with chemotherapy because, in the past, excess risks were established only after chemotherapy for cancers of the lung, ovary, breast, soft tissue, testis, and brain/central nervous system.

---

[368] https://www.cancer.gov/connect-prevention-study/
[369] https://seer.cancer.gov/
[370] https://seer.cancer.gov/statistics/videos/
[371] https://www.cancer.gov/news-events/cancer-currents-blog/2018/nci-seer-enhancements-creating-opportunities
[372] Morton LM, et al. *JAMA Oncol.* 2019 Mar 1;5(3):318-325. PMID: 30570657.

According to a new study, mortality rates from the most common lung cancer, non-small cell lung cancer (NSCLC), have fallen sharply in the U.S. in recent years, due primarily to recent advances in treatment.[373] Survival rates improved for patients diagnosed with NSCLC from 2001 to 2014; similar improvements were observed for men and women and across all races and ethnicities.[374] This analysis shows for the first time that nationwide mortality rates for NSCLC are declining faster than its incidence, an advance that correlates with the beginning of routine genetic testing in 2012 to determine which patients would benefit from recently approved NSCLC targeted therapies.

Ten to twenty percent of lung cancers develop in patients who have never smoked (called never smokers), and while environmental factors may play a role in some of these cancers, scientists are still unsure of the cause of most of these lung cancers. A genomic analysis of lung cancer in people with no history of smoking has found that a majority of these tumors arise from the accumulation of mutations caused by natural processes in the body.[375] Lung cancers in never smokers are heterogenous and this study describes, for the first time, three different molecular subtypes of lung cancer in people who have never smoked.[376]

GWAS have identified hundreds of variations in the human genome that confer a low-risk of developing cancer across types. NIH-supported researchers analyzed data from multiple GWAS to estimate the number and effect size of common genetic variants associated with risk for 14 cancers in adults with European ancestry.[377] Their findings support the accumulating evidence that cancer is a highly polygenic disease, meaning that many genes contribute to disease development, and provide a roadmap for potential future clinical use of polygenic risk prediction to stratify levels of risk of developing cancer throughout the population.

While it is known that African Americans are disproportionately impacted by colon cancer incidence and mortality rates compared to people of European descent, the underlying reason was not well understood. A recent study found that the right side of the colon ages biologically faster than the left side in both African Americans and people of European descent.[378] However, the right-side ages significantly faster in African Americans, suggesting why African Americans are more likely to develop cancerous lesions on the right side and are more likely to have early onset CRC. This is the first study to find race and side-specific differences in aging of normal colon, suggesting more research is needed with patients of African American descent to develop better ways to treat and prevent colon cancers across ethnic or racial groups.

[373] https://www.cancer.gov/news-events/press-releases/2020/lung-cancer-treatments-mortality-drop
[374] Howlader N, et al. *N Engl J Med.* 2020 Aug 13;383(7):640-649. PMID: 32786189.
[375] https://dceg.cancer.gov/news-events/news/2021/sherlock-lung
[376] Zhang T, et al. *Nat Genet*. 2021 Sep;53(9):1348-1359. PMID: 34493867.
[377] Zhang YD, et al. *Nat Commun.* 2020 Jul 3;11(1):3353. PMID: 32620889.
[378] Devall M, et al. *J Natl Cancer Inst.* 2020 Dec 30;113(12):1779–82. PMID: 33377907.

Since 2014, e-cigarettes have been the most commonly used tobacco product among U.S. middle and high school students.[379] In 2019, one in four high school students reported current use of e-cigarettes.[380] Studies have found that teenagers who vape nicotine may be more likely to go on to smoke traditional cigarettes.[381] Part of *Smokefree.gov*, *SmokefreeTeen* provides tools, tips, and information to quit tobacco and vaping.[382] As a result of significant gains in web and social media referrals and better search engine optimization, the *SmokefreeTeen* website experienced a 143 percent increase in users and 147 percent increase in sessions in FY 2019 over the same time period in FY 2018.

Environmental Health

Environmental health sciences research at the NIH aims to align with real-world public health needs and to translate science findings into knowledge that can inform real-life individual and public health outcomes. Environmental health sciences research includes research on how factors, including chemical, physical, synthetic, and infectious agents, social stressors, diet and medications, and our own microbiomes, among others, affect biological systems, sometimes causing diseases like cancer.

In FY 2019, the National Toxicology Program (NTP) celebrated 40 years as a program by reflecting on past achievements and continuing progress in advancing the science of toxicology.[383] NTP is a component of NIEHS and is an interagency partnership organization. In its early days, NTP and toxicology generally relied on animal testing and focused on identifying individual chemicals dangerous to human health. A lot has changed in 40 years, leading to NTP becoming the most trusted source of toxicology knowledge worldwide.

Per- and poly-fluoroalkyl substances (PFAS) are a large group of synthetic chemicals found in a variety of consumer products that have been linked to immune dysfunction, altered metabolism, brain development, and certain cancers. A recent study showed that exposure to PFAS in the womb may increase liver injury risk in children; this is the first study to examine the impact of early life exposures to a PFAS mixture on child liver injury.[384] The study used data from 1,105 mothers and their children enrolled in the Human Early-Life Exposome (HELIX) study in Europe. Using computational modeling, the scientists found that higher exposures to PFAS during pregnancy were associated with higher levels of liver enzymes in children. High liver enzyme levels may lead to nonalcoholic fatty liver disease (NAFLD). The researchers also identified a profile for children at high risk for liver injury, characterized by high prenatal PFAS exposures.

There is a growing body of evidence showing an association between environmental exposures—such as through air, water, food, soil, dust, or other environmental media—and breast cancer. Studies which enrolled women at higher breast cancer risk through family history, younger age of onset, and/or genetic

---

[379] Arrazola RA, et al. Tobacco use among middle and high school students—United States, 2011–2014. MMWR Morb Mortal Wkly Rep 2015;64:381–5. PMID:25879896.
[380] Cullen KA, et al. *JAMA* 2019 Dec 3;322(21):2095-2103. PMID: 31688912.
[381] https://newsinhealth.nih.gov/2020/05/risks-vaping
[382] https://teen.smokefree.gov/
[383] https://factor.niehs.nih.gov/2019/1/feature/3-feature-anniversary/index.htm
[384] Stratakis N, et al. *Hepatology.* 2020 Nov;72(5):1758-1770. PMID: 32738061.

susceptibility, consistently demonstrated an association between environmental chemical exposures and breast cancer risk.[385] In another study that used data from the National Air Toxics Assessment and the Sister Study,[386] a prospective study of risk factors for breast cancer and other diseases, NIH scientists found that airborne toxic substances, especially methylene chloride, which is used in aerosol products and paint removers, are associated with increased risk of breast cancer.[387] The study also suggested the association between certain airborne toxics and breast cancer appeared stronger in women who were overweight or obese.

Patients with type 2 diabetes (T2D) may have increased breast cancer risk, although use of the diabetic drug metformin may reduce that risk. A team led by NIH researchers found that women with T2D and long-term metformin use were 38 percent less likely to develop estrogen receptor (ER)-positive breast cancer compared with women without T2D.[388] However, women with T2D and metformin use were at increased risk of ER-negative breast cancer and triple-negative breast cancer. The scientists used data from 44,541 women in the Sister Study. The increased risk for ER-negative breast cancer and triple-negative breast cancer suggests that metformin does not protect against these breast cancer subtypes, perhaps due to differences in how subtypes of breast cancer develop.[389]

The Breast Cancer and Environment Research Program (BCERP) supports the enhancement of knowledge regarding environmental and genetic factors underlying breast cancer risk over women's lifespans and provides evidence-informed educational materials to mothers with daughters to help them engage in lifestyle changes to reduce their environmental risk of breast cancer.[390] In FY 2021, BCERP researchers developed and disseminated materials via social media, teaming up with racially and ethnically diverse mommy bloggers and readers to evaluate the cultural appropriateness of the information and message design.[391] The findings support the notion that the larger family system and cultural appropriateness should be considered when disseminating cancer risk education.

Using data from the Sister Study, scientists reported that increased intake of processed meat and use of high temperature to cook red meats increased the risk of CRC in women.[392] This study supported previous hazard assessments on processed meat and added information on CRC risks associated with specific processed meat products and cooking practices. Bacon was found to be associated with the highest risk of getting CRC, with a twofold increase in risk, followed by consumption of breakfast sausages. In terms of cooking practices reported for steaks and burgers, grilling/barbequing was associated with elevated risk of cancer.[393]

---

[385] Zeinomar N, et al. *Environ Res*. 2020 Aug;187:109346. PMID: 32445942.
[386] https://sisterstudy.niehs.nih.gov/English/index1.htm
[387] Niehoff NM, et al. *Environ Int.* 2019 Sep;130:104897. PMID: 31226564.
[388] Park YM, et al. *Ann Oncol.* 2021 Mar;32(3):351-359. PMID: 33516778.
[389] https://factor.niehs.nih.gov/2021/4/papers/dir/index.htm#a5
[390] https://bcerp.org/
[391] Fisher CL, et al. *J Cancer Educ.* 2021 Apr;36(2):284-293. PMID: 31820415.
[392] Mehta SS, et al. *Cancer Epidemiol Biomarkers Prev.* 2020 Jan;29(1):141-150. PMID: 31575555.
[393] https://factor.niehs.nih.gov/2019/12/papers/dir/index.htm#a1

Radiation of certain wavelengths, called ionizing radiation, has enough energy to damage DNA and cause cancer. Ionizing radiation includes radon, x-rays, gamma rays, and other forms of high-energy radiation. Lower-energy, non-ionizing forms of radiation, such as visible light and the energy from cell phones, have not been found to cause cancer in people.[394]

The Chernobyl disaster of 1986 in northern Ukraine exposed thousands of people to high levels of ionizing radiation, yet long term impacts of this exposure are debated. In two landmark studies, researchers used cutting-edge genomic tools to investigate the potential health effects of exposure to ionizing radiation from the accident at the Chernobyl nuclear power plant.[395] One study documented the genetic changes in the tumors of people who developed thyroid cancer after being exposed as children or fetuses to the radiation released by the accident.[396] In the second study, researchers found no evidence that radiation exposure to parents resulted in new genetic changes being passed from parent to child.[397]

Most people are exposed to low doses of ionizing radiation from medical exposures like computed tomography (CT) scans, naturally occurring radiation (emitted from bedrock within the earth's crust and cosmic rays emitted by the sun), and occupational exposures to medical, aircrew, and nuclear workers. A key question for low-dose exposures is how much of the damage can be repaired and whether other mechanisms, including inflammation, also play a role. This critical question has been long debated for radiation protection standards. NIH researchers recently published a study where they found clear evidence of excess cancer risk from low-dose ionizing radiation.[398] The researchers systematically reviewed previous epidemiological studies to assess the magnitude of the risk and their findings are based on data from 26 studies.[399] The analysis showed that most of the studies reviewed were free from major bias and the summary risk estimates were statistically significant. The magnitude of cancer risk (per unit dose) for low-dose radiation was consistent with the dose-dependent cancer risk observed in populations exposed to very high doses of radiation, such as atomic bomb survivors.

Coordinating Cancer Research Through Infrastructure and Collaboration

When people think of the progress made in cancer research, they do not often realize the coordination that must take place to make scientific discovery possible. The ability to train the next generation of scientists to challenge paradigm, to facilitate large clinical trials across multiple sites and even countries to discover the next breakthrough treatment, and to combine diverse data types for analysis of large data sets to facilitate new discoveries in cancer prevention, treatment, and diagnosis, is no easy feat. Fortunately, during FY 2019–2021, NIH had many consortiums, networks, data commons, and training grants at its disposal to better coordinate cancer research to generate groundbreaking discoveries.

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) is a national effort to accelerate the understanding of the molecular basis of cancer through the application of large-scale proteome and

[394] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/non-ionizing-radiation
[395] https://dceg.cancer.gov/news-events/news/2021/genetic-effects-chernobyl
[396] Morton LM, et al. *Science.* 2021 May 14;372(6543):eabg2538. PMID: 33888599.
[397] Yeager M, et al. *Science.* 2021 May 14;372(6543):725-729. PMID: 33888597.
[398] https://dceg.cancer.gov/news-events/news/2020/low-dose-monograph
[399] Hauptmann M, et al. *J Natl Cancer Inst Monogr.* 2020 Jul 1;2020(56):188-200. PMID: 32657347.

genome analysis, or proteogenomics. CPTAC pioneered the integrated proteogenomic analysis of colorectal, breast, and ovarian cancers to reveal new insights into these cancer types.[400] In FY 2019, CPTAC researchers published a landmark community resource paper on colon cancer[401] and released four datasets[402] on pediatric brain cancer, kidney cancer, lung cancer, and endometrial (uterine) cancer. In FY 2021, CPTAC researchers identified molecular features that drive PDAC—the most common type of pancreatic cancer—development, including over 200 proteins with higher expression levels in pancreatic cancer cells compared to normal pancreatic cells, and also identified potential therapeutic targets downstream from *KRAS*, a gene driver of cancer development.[403]

Childhood cancers are classified as rare cancers because they make up a small percentage of the overall cancers diagnosed annually, and their clinical and prognostic data is often hard to access because it is stored at the institution where they are treated. The Childhood Cancer Data Initiative (CCDI) was launched in FY 2020 to facilitate and accelerate progress in childhood, adolescent, and young adult cancer research through optimizing collection, utility, and sharing of clinical care and research data from all patients and survivors.[404] This includes developing a pediatric cancer data ecosystem of repositories, registries, and critical tooling to share and analyze data. In the first year, NCI's Board of Scientific Advisors, with the assistance from a Working Group of experts, reported 24 recommendations to NCI leadership for guiding the planning and implementation of future activities for CCDI. In its second year, critical work was done to establish an infrastructure to collaborate and learn from the wider childhood cancer community through focused groups that provide a variety of community perspectives to NCI leadership for guiding the planning and implementation of future CCDI activities.

The mission of the Early Detection Research Network (EDRN), established in 2000, is to discover, develop, and validate biomarkers and imaging methods to detect early-stage cancers and then further develop them into clinical tests.[405] ERDN support has led to eight FDA approved diagnostic tests or devices for clinical use and 18 biomarker tests that are available in Clinical Laboratory Improvement Amendments (CLIA) approved laboratories; CLIA regulates human laboratory testing. In 2021, EDRN was renewed for a record fourth time and was commended for its accomplishments and leadership, measures to improve biomarker discovery and validation, and emphasis on quality control and data replication for all candidate biomarkers. Additionally, the American Association for Cancer Research's journal *Cancer Epidemiology, Biomarkers and Prevention* published a special issue on the 20th anniversary of EDRN in 2020.[406]

NIH also established a new clinical trials network to perform early phase cancer prevention clinical trials that bridge the gap between preclinical agent development and phase 3 definitive efficacy trials. The Cancer Prevention Clinical Trials Network (CP-CTNet) conducts trials that assess the safety, tolerability,

---

[400] https://proteomics.cancer.gov/programs/cptac
[401] https://proteomics.cancer.gov/news_and_announcements/cptac-researchers-analyze-colon-cancer-proteins-and-genes-uncover-new
[402] https://proteomics.cancer.gov/data-portal
[403] Cao L, et al. *Cell.* 2021 Sep 16;184(19):5031-5052.e26. PMID: 34534465.
[404] https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative
[405] https://edrn.nci.nih.gov/
[406] Srivastava S, Wagner PD. *Cancer Epidemiol Biomarkers Prev.* 2020 Dec;29(12):2401-2410. PMID: 32357955.

and cancer preventive potential of agents and interventions of varying classes, many of which target molecules or processes known to be important for cancer development and growth.[407] These trials include phase 0 (micro-dosing), phase 1 (dose-finding), and phase 2 (preliminary efficacy) clinical trials. CP-CTNet strives to identify safe and effective preventive interventions to advance their further clinical development for cancer prevention.

In FY 2021, NCI launched the Early-Stage Surgeon Scientist Program (ESSP), which is designed to train surgeon scientists and retain them in cancer research by supporting a program focused on cancer-related disease and basic/translational research.[408] This program aims to bring together surgeon scientists from across the U.S. and build cohorts that will be trained together for up to three years. The ESSP participants will be funded through an administrative supplement to an NCI-designated Cancer Center Support Grant (P30) or Comprehensive Partnerships to Advance Cancer Health Equity grant (U54) to one of the institutions serving underserved health disparity populations and underrepresented students.

To provide clinicians with a more individualized approach to patient treatment, the Precision Medicine Analysis and Coordination Center (PMACC) was formally launched in 2020. The primary purpose of PMACC is to provide a precision medicine data center that will use data from various sources to recommend patients to therapeutic clinical protocols based on specific molecular targets, oncogenic pathways, and immune parameters, rather than disease type, for precise therapy assignment. The PMACC provides this support via the Molecular Analysis for Therapy Choice (MATCH) precision medicine platform that includes automated patient and trial management, algorithm-driven treatment assignment, and associated bioinformatics, computational biology, and data analysis services.[409]

Launched in FY 2020, the Cancer Research Data Commons (CRDC) is a cloud-based expandable data science infrastructure that connects data sets with analytics tools to allow users to share, integrate, analyze, and visualize cancer research data to drive scientific discovery.[410] The users of CRDC are biomedical researchers, tool developers, and data scientists. The CRDC provides access to data-type specific repositories: genomic, proteomic, human clinical trials, canine clinical trials, comparative oncology, imaging, and others. CRDC also provides access to programs such as TCGA and its pediatric counterpart, Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and CPTAC. The ability to combine diverse data types and perform cross-domain analysis of large data sets facilitates new discoveries in cancer prevention, treatment, and diagnosis, and supports the goals of precision medicine and the Cancer Moonshot[SM].

The Affordable Cancer Technologies (ACTs) Program supports innovative research on key scientific issues in global cancer control and leverages unique scientific opportunities afforded by global collaboration.[411] The ACTs Program supports resource-appropriate translational technology research and development for cancer, while ensuring affordability and potential impact in low-resource settings as essential design

[407] https://prevention.cancer.gov/major-programs/cancer-prevention-clinical-trials-network
[408] https://www.cancer.gov/grants-training/training/funding/nci-essp
[409] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match
[410] https://datacommons.cancer.gov/
[411] https://www.cancer.gov/about-nci/organization/cgh/research-training-programs/affordable-cancer-technology

components. The ACTs Program develops technology through every stage, from prototype to clinical implementation studies. The technologies are validated in real-world health settings, specifically in low- and middle-income countries (LMICs), leading to additional innovation. Examples of important elements include technologies that can be used by minimally trained health workers and technologies that are appropriate at the clinical point of need or are adaptable to diverse environmental conditions and health systems. Evaluation of the ACTs Program led to a renewal of the program for an additional five years in FY 2021.

The NCI Community Oncology Research Program (NCORP) is a national network of institutions that conduct clinical trials and cancer care delivery research in the community, where most cancer patients receive their care.[412] The NCORP network designs and conducts cancer prevention, supportive care and symptom management, screening, and surveillance clinical trials. The network also participates in treatment and imaging clinical trials conducted by the National Clinical Trials Network and integrates health disparities research questions into NCORP studies. In FY 2019, NCORP launched its second cycle of funding for a six-year funding period of 32 community sites, 14 minority/underserved community sites, and seven research bases, having accrued more than 35,000 patients in its first funding cycle.

The Cancer Community Partnership, established in FY 2020, will connect the scientific and medical community with individuals personally affected by cancer.[413] It aims to foster collaboration between individuals affected by cancer, patient advocates, researchers, and health care providers to learn from one another through inclusive conversations and to influence the development of cancer science and cancer care by integrating the patient experience at all levels. The Cancer Community Partnership is a learning community with three primary goals: for early career scientists to learn about the patients' perspectives and develop skills around communicating with a lay audience, for individuals affected by cancer to have an opportunity to share their experiences, and for research advocates to share the collective patient perspective and help advance science. The ultimate goal is to bring together people from across the cancer continuum to learn from another.

Cancer has no geographic borders; thus, NIH established a new international initiative, the Cancer Grand Challenges (CGC), with Cancer Research UK to address profound and unanswered questions in cancer research.[414] Challenges are identified through a series of international workshops to receive input from thought leaders across the cancer research community. Unique in scale and ambition, the CGC program provides international, multidisciplinary teams the freedom to try bold, novel approaches in the pursuit of answers to cancer's toughest challenges. The program is designed to inspire the brightest minds across the globe to come together and tackle these challenges on a grand scale.

[412] https://ncorp.cancer.gov/
[413] https://www.cancer.gov/grants-training/training/about/cancer-community-partnership
[414] https://www.cancer.gov/grants-training/grants-funding/cancer-grand-challenges

Neuroscience

An estimated 200 million Americans each year suffer from at least one neurological disorder, and as the population ages overall, the incidences of many of these disorders is increasing.[415] These disorders include neurodegenerative diseases, brain and spinal cord injuries, pain disorders, developmental disorders, and neuromuscular and movement disorders, and they impact people across the lifespan. The prevalence of these disorders has a huge economic and personal impact, and while research on risk, prevention, and treatment is ongoing, NIH investment in research in these areas remains critical. As the brain and nervous system impact and connect to every other part of the body—controlling cognition, movement, behavior, and basic functions like respiration—it is vital that NIH-supported scientists continue to develop a detailed understanding of how these systems function, and any conditions that impact the ability of these systems to function properly. Furthermore, neuroscience research plays an essential role in understanding and treating mental health disorders, including substance use disorders.

Summary of NIH Activities

Funding neuroscience research is central to the mission of several NIH ICs, including NIA, NICHD, NIDA, NIDCD, NIMH, and NINDS. Although each NIH IC has a well-defined mission with respect to disease, several NIH components support complementary programs of basic neuroscience research that advance the missions of all. In addition, other ICOs that fund neuroscience include the NIH Common Fund, NCCIH, NEI, NHLBI, NIAID, NIAMS, NIBIB, NIDA, NIEHS, and NINR. NIH spent $9,468 million on Neurosciences in FY 2019, $10,122 million in FY 2020, and $10,716 million in FY 2021.[416]

The NIH BRAIN Initiative is managed by the ten ICs whose missions and current research portfolios align with the goals of the initiative: NCCIH, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIMH, NINDS, and OBSSR within the NIH Office of the Director.[417] The BRAIN Initiative, launched in 2013, supports groundbreaking scientific projects. Many of the accomplishments mentioned throughout this section on neuroscience research were funded, either in part or completely, through the BRAIN Initiative. Through 2021, NIH has funded more than 1,100 awards to hundreds of investigators with a cumulative total investment of over $2.4 billion.[418] These awards support projects by individual laboratories and cross-disciplinary, team-based science, and cutting-edge technology development. The BRAIN Initiative has been increasing investments in diversity and inclusion, as well as in dissemination of tools, training, and data resources that will energize the entire neuroscience research community. In 2019, the ACD BRAIN Initiative Working Group 2.0 and BRAIN Neuroethics Subgroup provided strategic guidance on how best to carry out this ambitious vision in view of rapid advances and emerging opportunities.

Another key initiative includes the Autism Centers of Excellence (ACEs) which supports large-scale multidisciplinary studies on autism spectrum disorder (ASDs), with the goal of determining the causes and

[415] GBD 2017 US Neurological Disorders Collaborators, et al. *JAMA Neurol*. 2021 Feb 1;78(2):165-176. PMID: 33136137.
[416] https://report.nih.gov/funding/categorical-spending#/
[417] https://www.ninds.nih.gov/sites/default/files/documents/BRAIN_Initiative_Technical_Summary_Flyer_508C.pdf
[418] https://braininitiative.nih.gov/news-events/blog/nih-brain-initiative-director-outlines-new-era-transformative-projects-cell

best treatments for the ASD.[419] The ICs involved in the ACEs also participate in the NIMH-led Interagency Autism Coordinating Committee (IACC). Among other topics, ACE projects are focused on studying the earliest brain and behavioral markers of ASD, identifying ASD subtypes, understanding the differences between males and females with ASD, evaluating screening practices for ASD, and developing innovative interventions. Please see Chapter 4 for a full update on the ACEs.

NIH also seeks to provide scientific solutions to the opioid crisis through the HEAL Initiative.[420] Launched in 2018, the NIH HEAL Initiative® initially funded about 500 projects aiming to provide rapid scientific solutions to the national crisis of opioid addiction, overdose, and pain. HEAL has grown and adapted to the evolving and increasingly dangerous crisis. Through 2021, NIH funded more than 700 awards to hundreds of investigators in all 50 states, totaling nearly $2 billion in research. Almost every NIH institute administers HEAL research, which includes projects on enhancing pain management and improving prevention and treatment for opioid misuse and addiction.

NIH is also enabling some of the nation's leading scientists to tackle the problem of Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD) at an incredible scale and pace.[421] Several neuroscience advances are discussed in the subsections below, and additional examples can be found throughout other sections of Chapter 3.

Understanding the Biology of the Brain

Researchers regularly discover new key facets that explain how the brain and nervous system function. NIH has a key role in supporting basic research to understand how these systems operate and which mechanisms are implicated in disease and disorders. Neuroscientists study nervous system function and dysfunction on many different levels; they examine nerve cells, nerve networks, brain structures, and systems individually and collectively to develop a better understanding of how these components interact to perform different functions. Basic research is essential for long-term progress against neurological diseases and is essential to the NIH mission.

The Developing Brain

Critical to understanding the basic functions of the brain is understanding how the brain and nervous system develops and changes over time. Atypical nervous system development can lead to dysfunction not just in thoughts, emotions, and behavior, but can also impact very basic functioning across the body. Some key areas of research include the impact of the environment, including maternal health, on the development of infants and children, intellectual and developmental disorders, and genetic disorders. Additional developmental research is included in the Life Stages, Human Development, and Rehabilitation Section of this chapter.

The Adolescent Brain Cognitive Development℠ (ABCD) Study is the largest long-term study of brain development and child health in the U.S. It includes more than 11,000 children who were recruited when they were nine to ten years old and will be followed through adolescence at research sites across the

[419] https://www.nichd.nih.gov/research/supported/ace
[420] https://heal.nih.gov/
[421] https://www.ninds.nih.gov/current-research/focus-disorders/focus-alzheimers-disease-and-related-dementias

country.[422] The study aims to gain a deeper insight into normal brain development and outcomes as well as the effects of individual, familial, or environmental influences, including drug exposure. The results of these studies will provide families, educational systems, health professionals, and policymakers with practical information to promote the health, well-being, and success of children. Scientific results have already started to come out of ABCD research. For example, one NIDA-funded study in 2020 showed that children with greater access to resources, better social support, and better perinatal health had larger brain surface areas and higher cognitive scores, regardless of family income.[423] The study also found that cognitive performance increased progressively with resources for children from families with high socioeconomic status, but only at the highest resource levels for children from families with low socioeconomic status.

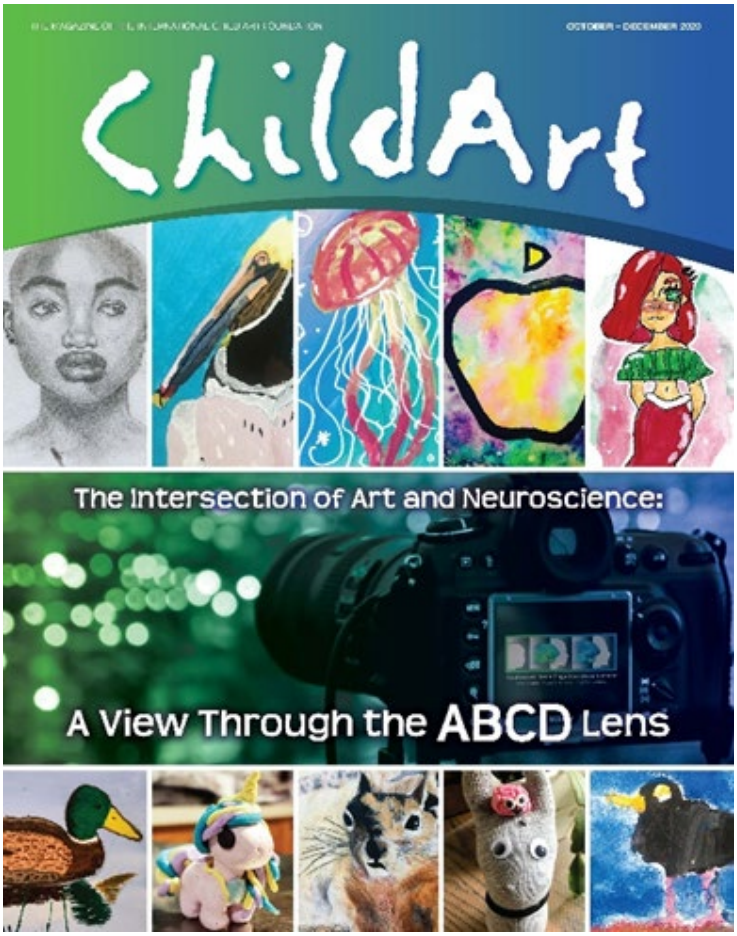


Figure 18: Cover of ChildArt magazine featuring ABCD-related art. Credit: Image Courtesy of ChildArt Magazine and NIH ABCD Study®

[422] https://nida.nih.gov/drug-topics/adolescent-brain/longitudinal-study-adolescent-brain-cognitive-development-abcd-study

[423] Gonzalez MR, et al. *Front Hum Neurosci*. 2020 Oct 28;14:578822. PMID: 33192411.

In another large-scale study designed to better understand brain development, the HEALthy Brain and Child Development study, funded in part by the HEAL Initiative,[424] is establishing a large cohort of pregnant women from regions of the country significantly affected by the opioid crisis and following them and their offspring into early childhood. This study is enabling researchers to collect information on normal brain development, the influence of genes and diverse social environments on this development, and the long-term impact of pre- and postnatal drug use.[425,426] It will also identify protective and resiliency factors that may ameliorate the effects of these exposures and inform the development of early interventions.

In addition to studying how environmental factors impact brain development, researchers have been investigating the genetic components of the development of neurologic disorders. Genetics have been linked to cerebral palsy, a disabling brain disorder for which there are no cures. Genes control how brain circuits are wired in early development. Results from the largest genetic study of cerebral palsy ever conducted estimate that about 14 percent of all cases may be linked to a patient's genetic changes and their impact on brain development.[427]

Genes also play a role in the development of stuttering. Stuttering is a speech disorder characterized by pauses and repeated or prolonged sounds, syllables, or words that disrupt the normal flow of speech. The condition is most commonly seen in young children, who typically outgrow the problem. However, for one in four children who experience early stuttering, the condition persists as a lifelong communication problem, and an estimated 1 percent of adults in the U.S. are affected by stuttering. NIDCD researchers identified changes in the brain brought on by a gene mutation previously linked to stuttering.[428] The scientists made this discovery by engineering one of the human stuttering gene mutations into mice and then studying the mouse vocalizations. They found that mice that had the mutation had long pauses in their streams of vocalizations, somewhat similar to those found in the speech of people with the same mutation. The scientists also noticed these mice had a loss of astrocytes, a type of brain-supporting cell, in the corpus callosum, which is a part of the brain that enables communication between the brain's left and right hemispheres. The corpus callosum helps integrate signals for processes that involve both hemispheres, such as physical coordination and use of language. The identification of genetic, molecular, and cellular changes that underlie stuttering has led scientists to understand persistent stuttering as a brain disorder.

To better understand brain development and behavior, researchers are developing new tools to precisely chart and modulate connections in the brain, helping to create detailed maps of the neural circuits involved in complex behavior. NIMH-supported investigators discovered that the brain's cerebellum, known to play a role in motor coordination, also helps control the neural circuity associated with social behavior and responses to rewards.[429] In another NIMH-funded study, researchers analyzed brain connectivity using functional magnetic resonance imaging (fMRI) to identify significant differences in the

[424] https://heal.nih.gov/
[425] https://nida.nih.gov/research/nida-research-programs-activities/healthy-brain-child-development-study
[426] https://heal.nih.gov/research/infants-and-children/healthy-brain
[427] Jin SC, et al. *Nat Genet*. 2020 Oct;52(10):1046-1056. PMID: 32989326.
[428] Han TU, et al. *Proc Natl Acad Sci U S A*. 2019 Aug 27;116(35):17515-17524. PMID: 31405983.
[429] Carta I, et al. *Science*. 2019 Jan 18;363(6424):eaav0581. PMID: 30655412.

brain circuitry associated with reward and arousal in children with anhedonia (loss of interest in or reduced ability to experience pleasure from activities), compared to children without anhedonia.[430] These studies are helping to elucidate the neural circuitry that drive behavior. Research on this neural circuitry could lead to better understanding of the mechanisms underlying mental illnesses and to the development of targeted neural circuit-based treatments in the future.

In addition to charting brain development, NIH researchers are also studying ways to detect disorders early. One team of NICHD-supported researchers recently developed a prototype app for mobile devices that can screen children at risk for ASD.[431] Researchers found that the app could distinguish toddlers diagnosed with ASD from typically developing toddlers by tracking their eye movements while watching videos. With more research, the app could one day screen infants and toddlers and refer them for early intervention, when chances for treatment success are greatest. In another NICHD-funded study, researchers investigated one proposed treatment for ASD: regular doses of the hormone oxytocin.[432] The researchers found that contrary to smaller-scale studies, this hormonal treatment does not appear to help children with ASD. From this larger study, healthcare providers now have more information on appropriate therapies, and this can contribute to the broader understanding of hormones on brain development.

Sensation and Perception

To better understand the biology of the brain and the broader nervous system, it is important to understand how the nervous system supports one's senses and how the brain processes that information into perception. Taste relies on receptors on the tongue responding to stimuli differently depending on the chemical and molecular components within a piece of food. The sensation and perception of sour was not well-understood previously. NIDCD-supported scientists have discovered and described the structure of the protein OTOP1, which impacts the sour taste receptor cells on the tongue.[433,434] Researchers have found that mice that lack the gene that is needed to make OTOP1 have reduced responses to sour-tasting liquids, providing evidence that these proteins play a critical role in detecting sour tastes on the tongue. This can provide insight as to why people seek out certain foods and avoid others.

To understand mechanisms that impact one's sense of smell, researchers have been investigating what cellular signals trigger stem cells in the nose to become certain types of cells such as nerve cells or supporting cells.[435] NIDCD-funded scientists used a sophisticated technique to track the genes expressed in single stem cells over time and found specific cellular signals that direct stem cells to become certain types of mature cells within the nose. This basic research may lead to treatments for people who lose their ability to smell and helps scientists understand how this impacts people without a good sense of smell.

---

[430] Pornpattananangkul N, et al. *JAMA Psychiatry*. 2019 Jun 1;76(6):624-633. PMID: 30865236.
[431] Chang Z, et al. *JAMA Pediatr*. 2021 Aug 1;175(8):827-836. PMID: 33900383.
[432] Sikich L, et al. *N Engl J Med*. 2021 Oct 14;385(16):1462-1473. PMID: 34644471.
[433] Saotome K, et al. *Nat Struct Mol Biol.* 2019 Jun;26(6):518-525. PMID: 31160780.
[434] Teng B, et al. *Curr Biol*. 2019 Nov 4;29(21):3647-3656.e5. PMID: 31543453.
[435] Fletcher RB, et al. *Cell Stem Cell*. 2017 Jun 1;20(6):817-830.e8. PMID: 28506465.

In both taste and smell, there is a connection between cells in the nose and mouth and the brain. Sensory systems transform sensations from the external world into neural activity. In the mouse, smelling different odors leads to changes in which group of neurons are activated, when neurons are activated relative to each other (synchrony), and how long it takes from the start of odor inhalation (latency) for neuron activation. To examine the relevance of each feature to olfaction, NIH BRAIN Initiative-funded investigators developed a holographic two-photon optogenetic stimulation method which allows researchers to observe single action potentials in cells.[436] They applied their new technique to olfactory perception and found that, in mice, synchrony, rather than latency, is key to sensory perception. This ultra-precise imaging approach has great potential in advancing our understanding of the neuronal dynamics of other sensory systems and behavior.

In addition to understanding the mechanisms underlying one's sense of smell in response to actual scent stimuli, phantom odor perception is something that 6.5 percent of Americans over the age of 40 experience.[437] Phantom odor perception is the sensation of an unpleasant, bad, or burning odor without an identifiable source. Understanding this disorder can help elucidate what impacts the perception of smell outside of neurons in the nose. Individuals who perceive phantom odors can have a marked reduction in quality of life. An NIDCD study found that middle-aged women were more likely to experience phantom odors compared to older women, and people with head trauma, those reporting dry mouth symptoms, and those in poorer health reported phantom odors more frequently. The study could inform future research related to the neural components of perception of phantom odors.

Beyond taste and smell, the perception of signals from within the body, such as respiration and hunger, is called interoception. Interoception is essential for cognition and emotions, and while previous research has indicated that the insular cortex of the brain plays a role in interoception, the circuit mechanisms driving it are not well understood. To better understand sensation within one's airways, which impacts respiration, researchers found specific neurons in the throat that act as a first line of defense in detecting whether anything has entered one's airway other than air. They also found neurons expressing the *P2RY1* gene were involved in airway defense. These neurons are part of a circuit that involves the insular cortex, providing additional evidence for its role in interoception.

To better understand specialized sensory nerves cells, NIH researchers developed a new technique using human stem cells to efficiently grow neurons in a dish.[438] Humans may have a specific kind of sensory neuron that can sense both cold temperature and mechanical force, but this type of neuron is not found in mice. It is therefore important to use stem cells to produce human-specific neurons in a laboratory setting enabling investigation of human biology, disease, and treatment in otherwise inaccessible tissue. The researchers applied this new method to generate sensory neurons from human patients with PIEZO2 deficiency, a rare genetic disorder. This disorder causes a lack of the senses of touch and body position (proprioception) from birth, and it also causes insensitivity to a category of chronic pain called mechanical allodynia. It was found that neurons derived from these patients are completely insensitive to mechanical

[436] Gill JV, et al. *Neuron*. 2020 Oct 28;108(2):382-393.e5. PMID: 32841590.
[437] Bainbridge KE, et al. *JAMA Otolaryngol Head Neck Surg*. 2018 Sep 1;144(9):807-814. PMID: 30128498.
[438] Nickolls AR, et al. *Cell Rep.* 2020 Jan 21;30(3):932-946.e7. PMID: 31968264.

stimulation, and that they can be genetically corrected using CRISPR-Cas9 to restore their mechanosensitivity. This new work builds on prior techniques to precisely generate individual subtypes of sensory neurons which could be used in drug development and studying human disorders of touch and pain.

As more is understood about the neurons underlying sensation, it is important to also study the connection between sensation and perception. Just as tasting and smelling have both sensory and cognitive components, pain also is driven by complex processes with both physical and cognitive components. Experiencing and preventing pain are also major drivers of behavior which have a serious impact on quality of life, thus, understanding the basic mechanisms driving pain and pain reduction are foundational research areas that can have wide implications for future treatment. NINDS and NIDA-funded researchers identified a group of neurons in the basolateral amygdala that link the negative feeling of pain to physical pain information.[439] Silencing these neurons during painful stimuli reduced emotional reactions to pain without affecting reflexes, anxiety, or reward-related behaviors. Investigators also found that these neurons were needed for experiencing the unpleasantness of neuropathic pain, a chronic pain condition.

In another recent study, researchers sought to identify how mindfulness impacts brain activity in response to pain.[440] Mindfulness is a form of meditation focusing on paying attention to the present moment without reacting to it. Previous studies have demonstrated that people who are naturally more mindful tend to have less pain; however, the mechanisms underlying this relationship have not been identified. This study showed that the greatest difference in brain activity between naturally high- and low-mindful participants was in regions of the brain involved in processing attention and emotional responses to sensations. The results of these studies could impact future approaches to pain management that do not involve opioid treatment and can treat acute and chronic pain without the risk of addiction.

Connections Across Systems

The body has many complicated systems that control functions from basic digestion and respiration to complex and multi-system behaviors. Neuroscience researchers investigate how the brain and the broader nervous system are connected to and can affect other organs and organ systems and their processes.

The connection between the brain and the gut has garnered a lot of recent research. To better understand the connection between stress and ulcers, researchers tracked the nerve connections between a rat's gut and the brain, and found that the brain areas that control rats' stomach responses to stress are the same areas of the brain involved in regulating emotion and interoception.[441] While there are definitely other factors that impact the development of stomach ulcers, this research sheds light on a mechanism for a significant psychosomatic contribution to stomach ulcer formation. Researchers have also found that people with cavernous angiomas (CA), which are abnormal bundles of brittle blood vessels in the brain or

[439] Corder G, et al. *Science.* 2019 Jan 18;363(6424):276-281. PMID: 30655440.
[440] Zeidan F, et al. *Pain*. 2018 Dec;159(12):2477-2485. PMID: 30015711.
[441] Levinthal DJ, et al. *Proc Natl Acad Sci U S A*. 2020 Jun 9;117(23):13078-13083. PMID: 32434910.

spinal cord, also have specific bacteria in their gut.[442] Using advanced genomic analysis techniques, researchers found that the relative abundance of three gut bacterial species distinguished CA patients from controls, regardless of other factors. CA patients also showed more gram-negative bacteria, whereas controls had more gram-positive bacteria.

In another study seeking to better understand the nervous system connection between the gut and the brain, investigators observed the vagus nerve. Previous research suggested that a pathological form of the protein implicated in Parkinson's disease (PD) dysfunction, alpha-synuclein (alpha-syn), travels from the gut to the brain via the vagus nerve, but this had yet to be proven. To test this theory, NINDS-funded scientists injected synthetic alpha-syn into the guts of healthy mice.[443] Over the course of ten months, they found that the alpha-syn spread from one brain region to the next in a predictable pattern that mimicked neurodegeneration seen in human PD patients. When investigators severed the vagus nerve, they prevented the gut-to-brain spread and associated behavioral dysfunction. These results may offer a new, more precise method to test treatments that could prevent or halt PD in humans.

Additional connections between the brain and gut have been found in a study of immune cells in the brain's meninges.[444] Researchers studied mouse and human postmortem tissue and found Immunoglobulin A (IgA) cells, which are antibody-producing cells typically found in mucous membranes of the bronchial tree of the lungs and gut, in the outer layer of the meninges. Genetic sequencing confirmed that the cells originated in the intestine, thus providing additional evidence for a close brain and gut connection.

There is also a growing appreciation that nerve cells collaborate with the immune system to augment immunity. NIH-supported researchers found experimental activation of pain-sensing nerves in the skin triggers a protective, type-17, inflammatory response in the immediate and adjacent skin areas triggered, even in the absence of microbial infection or tissue damage.[445] The discovery, that activated skin neurons transmit signals that prime adjacent unstimulated skin to resist infection, has important implications for understanding skin diseases such as psoriasis, in which type-17 skin immunity is exacerbated. A similar protective connection between the brain and immune system was found when researchers studied the immune mechanism that protects the brain from airborne viruses entering through the nose into the olfactory bulb.[446] Using fluorescent microscopy, researchers found the CD8 T cell type, protected the brain from a nasal virus infection by engaging immune cells within the central nervous system (CNS) to facilitate immune system recognition of the virus in a way that limited the damage to neurons. These findings on how the nervous system and immune system work together can impact the mechanisms future researchers build upon when developing treatments.

[442] Polster SP, et al. *Nat Commun*. 2020 May 27;11(1):2659. PMID: 32461638.
[443] Kim S, et al. *Neuron*. 2019 Aug 21;103(4):627-641.e7. PMID: 31255487.
[444] Fitzpatrick Z, et al. *Nature*. 2020 Nov;587(7834):472-476. PMID: 33149302.
[445] Cohen JA, et al. *Cell*. 2019 Aug 8;178(4):919-932.e14. PMID: 31353219.
[446] Moseman EA, et al. *Sci Immunol*. 2020 Jun 5;5(48):eabb1817. PMID: 32503876.

Advanced computational methods have also been used to further understand sleep.[447] Research supported by the NIH Common Fund's Illuminating the Druggable Genome program investigated how the MT1 protein interacts with melatonin to prepare humans for sleep. Researchers examined how over 150 million different chemicals interact with the MT1 protein and identified two new molecules that changed the functioning of the MT1 protein. The new molecules were able to shift a mouse's sleep cycle by 1.5 hours, demonstrating the potential for these findings to control melatonin biology and may have future implications for treatment of sleep disorders.

Identifying Risk Factors and Focusing on Prevention

There are many health risks that include characteristics, called risk factors, that impact whether a person's health risk is high or low. Some characteristics include age, family health history, and lifestyle.[448] While some risk factors can be changed, such as diet and physical activity, others, such as genetics, cannot be changed. Understanding how these characteristics impact health and how they interact with the environment to impact health can lead to prevention, early detection, and improved treatment of disease. Hypertension is a primary risk factor for the formation of white matter lesions associated with cognitive decline as well as Alzheimer's and related dementias. In a nationwide study, NIH-funded researchers used MRI to scan the brains of hundreds of hypertensive participants in the NIH Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT-MIND).[449] Investigators found that compared to standard blood pressure treatment, intensive blood pressure treatment reduced the accumulation of white matter lesions in participants. Intensive lowering of blood pressure did not significantly reduce dementia risk but did have a measurable impact on mild cognitive impairment. These results support a growing body of evidence suggesting that controlling blood pressure may not only reduce the risk of stroke and heart disease, but also of age-related cognitive loss. These results were the first to demonstrate an intervention that significantly reduces the occurrence of mild cognitive impairment, which is a well-established precursor of dementia.

Vascular risk factors, including high levels of dietary salt consumption, are associated with cerebrovascular disease and cognitive impairment. NINDS-funded investigators found that mice eating a high sodium diet showed symptoms of dementia due to changes in the gut.[450] Dietary salt induced cognitive decline in middle aged mice, effects that were prevented by restoring normal gut function. The study highlights the importance of factors such as diet and gut health in preventing the neurodegeneration that underlies dementia.

Genetic risk factors are also implicated in the development of neurologic diseases. Many people with Down syndrome develop AD with dementia when they get older. People with Down syndrome are born with an extra copy of chromosome 21, which carries a gene that produces the amyloid precursor protein (APP). Too much APP leads to a buildup of protein clumps called beta-amyloid plaques in the brain. The

---

[447] Stein RM, et al. *Nature*. 2020 Mar;579(7800):609-614. PMID: 32040955.
[448] https://newsinhealth.nih.gov/2016/10/understanding-health-risks
[449] SPRINT MIND Investigators for the SPRINT Research Group, et al. *JAMA*. 2019 Aug 13;322(6):524-534. PMID: 31408137.
[450] Faraco G, et al. *Nature*. 2019 Oct;574(7780):686-690. Erratum in: Nature. 2020 Feb;578(7793):E9. PMID: 31645758.

presence of beta-amyloid plaques is one of the hallmarks of AD, along with neurofibrillary tangles made of the protein tau. To find biomarkers that can diagnose and assess cognitive decline among aging adults with Down syndrome, scientists analyzed plasma samples from over 300 individuals with Down syndrome who were age 35 years and older.[451] This study is one of the first to confirm the link between biomarkers (in this case, the plasma neurofilament light chain and tau proteins), and AD in aging adults with Down syndrome. These blood biomarkers may be helpful for identifying adults with Down syndrome to participate in future clinical trials to prevent AD, based on their risk of developing dementia.

Pregnancy is also a risk factor for certain health conditions, especially when pregnant people have other disorders. To better understand health risks for pregnant women with epilepsy, NINDS-funded investigators from the longstanding Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) conducted a study to determine whether women with epilepsy have a higher seizure frequency during pregnancy than those who are not pregnant.[452] They found no meaningful difference between pregnant and nonpregnant individuals in seizure frequency. However, they did observe more frequent increases in doses of antiepileptic drugs in pregnant versus nonpregnant individuals in the study, which is a potential cause of concern and an area for future research. The impact of these drugs on the development of children born to these individuals is another area of research and potential risk factor. In another paper published from the MONEAD study, researchers found there is no difference in cognitive outcomes at age two among children of healthy individuals and children of individuals with epilepsy who took antiseizure medication during pregnancy.[453] However, children born to mothers with the highest levels of antiseizure medication in the blood during the third trimester had somewhat lower scores on tests in the motor and general adaptive domains, which refer to skills related to self-care, such as feeding. Results so far indicate that controlling epilepsy with these medications during pregnancy may be safe for babies. The results from these studies clarify the levels of risk associated with taking anti-seizure medicine while pregnant and can support clinicians in making decisions with their patients.

To better understand what contributes to a person's risk to develop a disorder or risk associated with treatments, researchers are also focusing on ways to prevent the development of disorders in the first place. New findings from the Atherosclerosis Risk in Communities Study (ARIC) of middle-aged adults add to the growing evidence base that physical activity is not only good for the heart, but also for the brain.[454] The researchers found that after 17 years of follow-up, participants who engaged in high levels and persistence of physical activity in midlife had about a 40 percent reduced incidence of dementia compared to their sedentary peers.

Improving Detection and Diagnosis

Effective diagnostic tests are critical tools to be able to confirm a neurological disorder or medical condition. New techniques and instruments are making diagnoses easier and less invasive than ever before. Doctors are now able to accurately diagnose diseases and track the impact of treatment on many

[451] Petersen ME, et al. *J Alzheimers Dis*. 2021;79(2):671-681. PMID: 33337378.
[452] Pennell PB, et al. *N Engl J Med*. 2020 Dec 24;383(26):2547-2556. PMID: 33369356.
[453] Meador KJ, et al. *JAMA Neurol*. 2021 Aug 1;78(8):927-936. PMID: 34096986.
[454] Palta P, et al. *Alzheimers Dement*. 2019 Feb;15(2):273-281. PMID: 30321503.

neurological diseases, allowing for improved treatment of disorders and facilitating further treatment development.

NIH established the second iteration of the Accelerating Medicines Partnership/Alzheimer's Disease (AMP-AD 2.0) in 2021.[455] This partnership among government, industry, and nonprofit organizations is transforming the current model for developing new diagnostics and treatments for AD. This program's goals include specific areas of research to expand, such as creating molecular profiles of the brain, cerebrospinal fluid, and blood samples from diverse cohorts. It also includes expanding dynamic models of disease trajectory and developing models of disease trajectory at a single-cell resolution. Data from AMP-AD are shared through the AD Knowledge Portal,[456] a platform for accessing data, analyses, and tools that the NIA Alzheimer's Disease Translational Research Program generates through several initiatives.

There is a critical need for biomarkers and diagnostics that can differentiate between different forms of dementia, especially those that are affordable and easy to administer in clinical practice. NIA-supported researchers have developed new blood tests that may be useful for diagnosing, or ruling out, AD in clinical settings. For example, PrecivityAD™, the first blood test for AD's characteristic amyloid protein, developed with NIA SBIR funding, recently became commercially available.[457,458] The PrecivityAD™ test is a highly sensitive blood test that uses mass spectrometry. Another blood test detects the abnormal accumulation of a form of tau protein known as phosphorylated-tau-181 (ptau181), was also developed by NIH-supported investigators.[459] Using this blood test, researchers were able to identify which patients had AD vs. frontotemporal dementia. Using these blood tests will allow for less costly and less invasive AD diagnoses. NIH supported researchers have also developed a new method to detect a protein biomarker for PD in skin with 96 percent sensitivity, enabling the development of a non-invasive diagnostic tool for PD.[460] Although these tests are not yet widely available outside of research settings, they show tremendous promise for speeding accurate diagnosis among people with early cognitive decline or other symptoms.

To better diagnose and understand the severity of Traumatic Brain Injury (TBI), a common injury that may result in cognitive and physical impairments, morbidity, and mortality, researchers have been investigating different biomarkers of neural injury. Researchers investigated the neurofilament light (NfL) and glial fibrillary acidic protein (GFAP), and the diagnosis, prognosis, severity, brain volume, and estimates of axonal injury following a TBI over several years and across different levels of severity of TBI.[461] They found that serum NfL is diagnostically useful in acute and repetitive sports-related concussions and in patients with TBI in terms of functional outcomes and grey and white matter volume in these patients,

[455] https://www.nia.nih.gov/research/amp-ad
[456] https://adknowledgeportal.synapse.org/
[457] https://www.nia.nih.gov/news/nih-small-business-funding-boosts-alzheimers-science-advances
[458] https://www.nia.nih.gov/news/blood-test-method-may-predict-alzheimers-protein-deposits-brain
[459] Thijssen EH, et al. *Lancet Neurol*. 2021 Sep;20(9):739-752. Erratum in: Lancet Neurol. 2021 Oct;20(10):e6. PMID: 34418401.
[460] Manne S, et al. *Mov Disord*. 2020 Dec;35(12):2230-2239. PMID: 32960470.
[461] Shahim P, et al. *Neurology*. 2020 Aug 11;95(6):e610-e622. Erratum in: Neurology. 2021 Mar 23;96(12):593. PMID: 32641538.

while GFAP is diagnostically useful at 30 days post-injury. These discoveries will improve the ways in which clinicians can diagnose TBI, interpret severity, and track changes over time.

Advancing Treatment

NIH seeks to improve health and reduce illness, thus it is critical to advance treatment for disorders. Neurological and neuropsychiatric disorders are complex, impacting many systems within the brain and body, and the mechanisms driving them are still being investigated. NIH continues to invest in research to develop novel treatments and improvements to patient and caregiver quality of life through molecular interventions, data sharing and collaborations, and technology development.

Alzheimer's has been recognized as a complex disorder that involves many cellular changes including the accumulation of proteins including amyloid beta protein (Aβ), tau, TAR DNA-binding protein 43 (TDP43), and alpha-synuclein in the brain, and the inflammation, genetics, environmental factors, and changes to the vascular system. NIA supports a wide range of studies designed to investigate the causes and treatments of Alzheimer's that include genetics and environmental studies (e.g., infectious agents and pollutants) as well as the involvement of inflammation, fat droplets, the vascular system, the cellular "garbage disposal systems" in our brains, and much more. NIA employs a broad and diverse approach to advance treatments for AD.[462]

Molecular Interventions

The emergence of high-throughput molecular and clinical technologies, combined with rapid growth in capacity to analyze enormous amounts of data, is providing unprecedented opportunities for investigating drug treatments for AD and ADRD.[463] To facilitate the identification of existing drugs that may be effective against AD/ADRD, NIA leads the Drug Repurposing for Effective Alzheimer's Medicines (DREAM) study, in which investigators work to identify metabolic abnormalities that underly, accelerate, or interact with the development of AD/ADRD pathology. Large patient cohorts are then mobilized to test whether drugs approved for other indications that also target metabolic drivers of AD/ADRD. Recently, researchers used this data-driven analysis method to identify two cancer drugs that reduced neuroinflammation and the development of amyloid plaques and tau tangles, two known hallmarks of AD, in cell culture models, suggesting that the drugs may be candidates for clinical trials. NIA-supported researchers found that bumetanide, a commonly-prescribed diuretic, may be a viable treatment for individuals at genetic risk of AD.[464]

In 2021, FDA granted accelerated approval of aducanumab (Aduhelm™) for the treatment of AD, marking a milestone in Alzheimer's research.[465] Aducanumab is an immunotherapy that targets amyloid plaques in the brain of people with Alzheimer's. It is the first FDA-approved treatment that addresses the underlying disease process to slow or reverse the progression of this condition, as well as the first Alzheimer's treatment to receive FDA approval of any kind since 2003. NIA supported much of

[462] https://www.nia.nih.gov/news/nia-statement-amyloid-beta-protein-dementia-research
[463] Roberts JA, et al. *Sci Adv*. 2021 Nov 12;7(46):eabi8178. PMID: 34757788.
[464] https://www.nih.gov/news-events/news-releases/precision-medicine-data-dive-shows-water-pill-may-be-viable-test-alzheimers-treatment
[465] https://www.nia.nih.gov/news/nia-statement-fda-approval-aducanumab-alzheimers-disease

aducanumab's preclinical development. Additional trials are ongoing to verify the clinical benefits of this new drug.

It is also sometimes the case that previous research has identified genetic mutations that lead to disorders and dysfunction, and now improved gene editing techniques allow for the investigation of potential treatment routes. Some hearing loss is caused by genetic mutations and limited or disordered hair cell growth within ears. To prevent hair cell death and the resulting progressive hearing loss in mice caused by an inherited gene mutation, NIDCD-supported scientists developed a novel approach to deliver a gene-editing complex into the inner ears of newborn mice by packaging the gene-editing complexes in lipids (fats) that form structures called liposomes. The liposome-packaged complexes move readily through cell membranes into cells. As a result, substantially more hair cells survived in the ears of treated compared to untreated mice which significantly reduced progressive hearing loss. This novel strategy may lead to new therapies for hearing loss caused by inherited genetic mutations.

Understanding Pathology to Develop Treatment

In addition to research on specific drugs and molecular interventions, NIH-funded researchers are investigating factors that impact the pathology of AD and cerebral amyloid angiopathy (CAA), which can lead to different treatment options. In AD and CAA, amyloid-beta protein fragments, or plaques, accumulate in the tissue and blood vessels of the brain. In mouse experiments, NINDS-funded researchers recently found that slow, spontaneous vessel pulsations, known as vasomotion, drive the clearance of waste products from the brain.[466] Vessel pulsations and clearance rates were hindered in mice with CAA. These results highlight the importance of vasculature in the pathophysiology of AD and may inform new therapeutic strategies that delay or prevent the onset of Alzheimer's and related diseases in humans.

Researchers also recently discovered accumulations of the TDP-43 protein, similar to those found in the brains of people with amyotrophic lateral sclerosis (ALS) and other neurodegenerative disorders, also occur in muscle tissue where they may play a beneficial role in regeneration.[467] This work demonstrates how a pathological structure in one disease or condition may serve a critical normal function in another organ and opens the door to new understandings for how to treat amyloid-associated degenerative diseases.

Other NIH-funded research is similarly focused on elucidating the mechanism that causes ALS with the goal of developing targeted treatment. By studying lab-grown neurons derived from the skin or blood cells of patients with ALS-causing mutations, as well as patients with non-inherited ALS, researchers have found a possible starting point for the dysfunction that causes the disease.[468] Researchers found an accumulation of the charged multivesicular body protein 7 (CHMP7) in the nucleus of ALS cultured nerve cells and in ALS samples from the brain region that controls movement. Treatments that decreased the amount of CHMP7 in the cultured cells prevented a series of abnormalities that are characteristic of ALS, providing a possible therapeutic target for the disease. NIH has also supported additional ALS research

[466] van Veluw SJ, et al. *Neuron*. 2020 Feb 5;105(3):549-561.e5. PMID: 31810839.
[467] Vogler TO, et al. *Nature*. 2018 Nov;563(7732):508-513. PMID: 30464263.
[468] Coyne AN, et al. *Sci Transl Med*. 2021 Jul 28;13(604):eabe1923. PMID: 34321318.

through the Accelerating Leading-edge Science in ALS (ALS^2) initiative, part of the NIH Common Fund's High-Risk, High-Reward program.[469,470] ALS^2 supported four new projects in 2021 focused on identifying the genetic and cellular factors that drive nerve cell death, determining how environmental exposures that may contribute to ALS disease risk interact with molecular and immune functions, investigating the restoration of the balance among key proteins that impact ALS as a treatment option, and determining how changes associated with ALS disease are linked to dysfunction in specific cell types.

Understanding the mechanisms driving neurodegeneration is another area of basic research that can have major implications for treatment development. In mice, loss of the enzyme topoisomerase 1 (TOP1) leads to DNA damage in neurons and neurodegeneration.[471] Researchers raised mice that were lacking TOP1 and found that these mice showed signs of early neurodegeneration, with brains 3.5-times smaller at postnatal day 15 compared with controls, showed motor deficits, and died prematurely. They also exhibited lower levels of nicotinamide adenine dinucleotide (NAD+)—a compound critical in energy metabolism. Researchers found that when mice lacking TOP1 received supplemental NAD+, they lived 30 percent longer, had less inflammation, and showed improved neuronal survival. DNA damage induced neurodegeneration is observed across neurodegenerative disorders, AD, PD, ALS, and ataxia-telangiectasia. Because DNA damage-induced neurodegeneration is frequently associated with hyperactivation of the NAD+ consuming enzyme, this research on mice contributes to the body of research that helps researchers better understand the mechanisms impacting these disorders.

NINDS leads the Blueprint Neurotherapeutics Network (BPN) for the NIH Blueprint for Neuroscience Research.[472] The BPN focuses on the discovery and development of small molecule drugs and biologic therapeutics and provides funding and resources to academic laboratories and small business enterprises to support lead optimization through phase 1 clinical testing. Successes to date include one compound tested in phase 2 clinical trials to improve cognitive and memory function in Fragile X Syndrome (FXS) and AD and another that has entered a phase 3 trial for Stargardt disease, an inherited juvenile form of macular degeneration. Another incubator designed to support innovators developing groundbreaking medical device technologies and help them overcome challenges along the translational path from bench to bedside is the Blueprint MedTech program.[473] The goal of this program is to accelerate the development of cutting-edge medical devices to diagnose and/or treat disorders of the nervous system, and to catalyze the translation of novel neurotechnologies from early-stage development to first-in-human clinical studies.

Clinical Trial Networks and Collaborations

Critical to the treatment approval process is the ability for researchers to conduct clinical trials. NIH supports several networks intended to facilitate collaborations toward the development of effective treatment and to support clinical trials necessary to determine whether those treatments are safe and

[469] https://commonfund.nih.gov/tra/als2
[470] https://www.ninds.nih.gov/News-Events/News-and-Press-Releases/Press-Releases/NIH-announces-new-Transformative-Research-Award
[471] Fragola G, et al. *Nat Commun*. 2020 Apr 23;11(1):1962. PMID: 32327659.
[472] https://neuroscienceblueprint.nih.gov/neurotherapeutics/bpn-biologics
[473] https://neuroscienceblueprint.nih.gov/neurotherapeutics/blueprint-medtech/blueprint-medtech

effective. The Network for Excellence in Neuroscience Clinical Trials, or NeuroNEXT, was created to conduct phase 2 clinical trials of treatments for neurological diseases through partnerships with academia, private foundations, and industry.[474] NeuroNEXT was designed to increase efficiency of clinical trials, expand the capability of NINDS to test promising new therapies, and respond quickly to opportunities to test promising new treatments for people with neurological disorders. NIH also supports the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN), which is a clinical trials network funded by NINDS, NHLBI, and NCATS.[475] The goal of the SIREN Network is to improve the outcomes of patients with neurologic, cardiac, respiratory, and hematologic emergencies by identifying safe and effective treatments given in the earliest stages of care.

NINDS established the StrokeNet to facilitate the rapid initiation and efficient implementation of small and large multisite exploratory and confirmatory clinical trials focused on promising interventions for stroke prevention, treatment, and recovery, as well as validation studies of biomarkers or outcome measures.[476] Between FY 2019 and FY 2021, seven new clinical trials started and are currently enrolling participants.

The Stroke Preclinical Assessment Network (SPAN), launched in 2019, is a translational research network testing therapeutic interventions aimed at protecting vulnerable brain tissue after a stroke through standardized and rigorous multi-site studies overseen by a central coordinating center.[477] The ultimate goal of the network is to identify the most promising neuroprotective drugs or interventions that can be delivered prior to or in conjunction with proven therapies, and to provide data to inform future clinical studies of neuroprotective strategies.

NIH has also been supporting initiatives to collect and safely share data with researchers who are working to develop treatments for diseases. The Accelerating Medicines Partnership (AMP) program for PD has launched a data portal to provide de-identified information collected from 4,298 PD patients and healthy controls to researchers working to develop effective therapies for the disease.[478] The portal enables researchers to study complex data sets and perform genome-wide analyses at a scale previously impossible. AMP PD is a public-private partnership between NIH, FDA, industry, and non-profit organizations that is managed through the Foundation for the National Institutes of Health (FNIH). The goal of this partnership is to transform and accelerate drug development in PD by providing the expertise and support needed to determine which biomarkers show the greatest potential for predicting PD and the progression of the disease.

[474] https://neuronext.org/
[475] https://siren.network/about-siren
[476] https://www.nihstrokenet.org/
[477] https://www.nih.gov/news-events/news-releases/nih-launches-novel-nationwide-search-neuroprotective-stroke-therapies
[478] https://www.ninds.nih.gov/News-Events/News-and-Press-Releases/Press-Releases/AMP-launches-PD-data-portal

Similarly, in 2019, NIA launched two new research centers to help meet the urgent need for therapies that will effectively treat or prevent AD.[479] The Target Enablement to Accelerate Therapy Development for Alzheimer's Disease (TREAT-AD) centers are providing added infrastructure for developing high-quality research tools and technologies needed to validate and advance the next generation of drug targets for Alzheimer's. Data, research methodologies, and computational and experimental tools will be disseminated openly and free-of-charge to the broader research community, including academia and industry, for use in drug discovery and research to better understand the complex biology of the disease. Through these centers, scientists are advancing drug discovery for new targets to the point of attracting external partners who can take them into clinical development.

Figure 19: SPARC program graphic. Credit: NIH Common Fund

Beyond PD and AD, the NIH Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program is accelerating development of therapeutic devices that modulate electrical activity in nerves to improve organ function.[480] In the first stage of the program, SPARC supported the development of new tools and technologies, mapped the connections among a variety of different nerves and organ systems, and created a rich public resource (the SPARC Portal[481]) that provides scientists with cutting-edge information and tools. Building on these accomplishments, stage two of the SPARC program will focus on the anatomy and functional connectivity of the human vagus nerve, build a new ecosystem of open-specification neuromodulation device components, challenge the innovator community to prove new capabilities, and continue to share data and digital resources through the SPARC Portal. Through these complementary initiatives, SPARC will facilitate the development of new best-in-class bioelectronic medicine therapies.

Improving Care and Quality of Life

In addition to supporting drug development and other treatments, NIH supports research that aims to directly improve care and quality of life for patients and caregivers. Loss of the ability to speak can have devastating effects on patients whose facial, tongue, and larynx muscles have been paralyzed due to stroke or other neurological conditions.[482] Brain-computer interface (BCI) technology uses sensors to

[479] https://treatad.org/
[480] https://commonfund.nih.gov/SPARC
[481] https://sparc.science/
[482] Anumanchipalli GK, et al. *Nature*. 2019 Apr;568(7753):493-498. PMID: 31019317.

measure electrical signals in the brain to run a computer program that can translate those signals into words. Different NIH-funded research teams are all working to improve BCI technology in different patient populations. BRAIN Initiative-funded scientists used brain signals recorded from epilepsy patients who were speaking while being scanned to program a computer to mimic natural speech. Interestingly, simply miming the act of speaking provided sufficient information to the computer for it to recreate several of the same sounds. Other BRAIN Initiative-funded scientists have developed a BCI designed to restore the ability to communicate in people with spinal cord injuries and neurological disorders such as ALS.[483] The researchers focused on the part of the brain that is responsible for fine movement and recorded the signals generated when participants attempted to write individual letters by hand, training a machine learning (ML) computer algorithm to identify neural patterns representing individual letters. While demonstrated as a proof of concept in one patient so far, this system appears to be more accurate and more efficient than existing communication BCIs and could help people with paralysis rapidly type without needing to use their hands.

NIDCD-supported scientists have significantly improved the performance of a BCI device used by people with locked-in syndrome who have difficulty moving or speaking by developing a program that combines data collected from electrical signals in the brain and from tracking eye movement.[484] This hybrid system improved the accuracy and speed at which users could type words by glancing at a keyboard and using their thoughts. Future work will translate this technology from the lab into the clinic or home for individuals with locked-in syndrome, potentially helping them communicate more easily and effectively with physicians, caretakers, and family. These NIH-funded research advances could one day have a profound effect on the ability of certain patients to communicate and could greatly improve quality of life for paralyzed patients.

NIH further supports the translation of basic science into therapeutics through the NIDCD FOA that is intended to provide an avenue for basic scientists, clinicians, and clinical scientists to jointly initiate and conduct translational research projects which translate basic research findings into clinical tools for better human health.[485] The scope of this FOA includes a range of activities to encourage translation of basic research findings which will impact the diagnosis, treatment, and prevention of communication disorders.

As with BCI research, other treatment innovations are sometimes investigated in small or single-patient studies. Researchers supported by the BRAIN Initiative published a case report describing a groundbreaking approach for alleviating treatment-resistant depression in a 36-year-old woman.[486] Investigators implanted a pacemaker-like device capable of delivering therapeutic electrical impulses deep into the brain. The device recognized the specific pattern of brain activity associated with the patient's depressive symptoms and delivered electrical impulses to the brain circuit where it could provide the most relief. While more study is needed, this precision approach to deep brain stimulation therapy offered the patient immediate improvement that has lasted now for more than a year.

---

[483] Willett FR, et al. *Nature*. 2021 May;593(7858):249-254. PMID: 33981047.
[484] Kalika D, et al. *J Neural Eng.* 2017 Oct;14(5):056010. PMID: 28585523.
[485] https://grants.nih.gov/grants/guide/pa-files/par-18-533.html
[486] Scangos KW, et al. *Nat Med*. 2021 Oct;27(10):1696-1700. PMID: 34608328.

Another way that NIH supports innovation in improving the quality of life in patients is through the Improving Care for People with Alzheimer's Disease and Related Dementias Using Technology (iCare-AD/ADRD) Challenge.[487,488] Through this challenge, NIA sought to spur and reward the development of applications to improve coordination and/or navigation of care among this patient population and their caregivers. Three winners were selected in 2019, with the first prize awarded to MapHabit for developing a mobile device application that helps people with dementia follow simple commands to perform daily tasks, such as taking pills and brushing teeth. Please see Appendix J for more information on the challenge.

Also critical for improving care is improving training of medical personnel. A large study of more than 21,000 people found that training emergency medical services (EMS) agencies to implement prehospital guidelines for TBI may help improve survival in patients with severe head trauma.[489] Previous work suggested that preventing low oxygen, low blood pressure, and hyperventilation in people with head injury before patients arrived at the hospital could improve survival, but the guidelines had not been assessed in real-world conditions. EMS agencies across Arizona were trained in the TBI guidelines, and patient outcomes were compared before and after the guideline implementation. Implementing the guidelines helped double the survival rate of people with severe TBI and triple the survival rate in severe TBI patients who had to have a breathing tube inserted by EMS personnel.

Facilitating Research

Research is a collaborative effort improved by infrastructure designed to allow scientists to share data, methods, and results. Neurological diseases and disorders are complex and impact many people, so NIH seeks to support and facilitate research by providing resources to support effective collaboration.

One project in the NINDS Strategic Plan is the Common Data Element (CDE) Project, which works with the research community to develop data standards for neuroscientific clinical research.[490] Central to this project is the creation of common definitions and metadata sets so that information is consistently captured, recorded, and harmonized across studies.

As described throughout this section, NIH has established a vast research infrastructure to advance Alzheimer's and related dementias research.[491,492] Efforts in this area include launching a consortium for Alzheimer's clinical trials, research efforts to validate cognitive tests in a primary care setting, and genetics and genomics sharing and collaboration initiatives. Data from these initiatives are shared through the AD Knowledge Portal,[493] a platform for accessing data, analyses, and tools that the NIA Alzheimer's Disease Translational Research Program generates through several initiatives. The program encourages open-science collaborations to share resources early in the research life cycle. Additionally, through its NIA and NINDS Intramural Research Programs, NIH established the Center for Alzheimer's and Related Dementias

[487] https://www.nia.nih.gov/challenge-prize
[488] https://www.maphabit.com/
[489] Spaite DW, et al. *JAMA Surg*. 2019 Jul 1;154(7):e191152. PMID: 31066879.
[490] https://commondataelements.ninds.nih.gov/
[491] https://www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc
[492] https://www.nia.nih.gov/research/ad-genetics
[493] https://adknowledgeportal.synapse.org/

(CARD) in April 2020.[494] Through CARD and in collaboration with the broader research community, researchers work across scientific domains and disease boundaries to bridge basic, preclinical, and clinical research with the goal of accelerating translational research on these diseases. CARD investigators are creating new cellular models of Alzheimer's and other forms of dementia, using cutting-edge sequencing techniques to expand capacity to identify genetic variants of interest, developing innovative therapies to engulf the tau protein (a cellular hallmark of AD) and flush it out of the brain, and generating innovative technology products to support Alzheimer's researchers and collaborators in their data science needs.

Another set of NIH-supported centers, the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (IDDRCs),[495] employ advanced technologies to support a broad range of research projects related to intellectual and developmental disabilities (IDDs). Centers have cores to provide infrastructure support, and they also support new research component projects, outcomes measures for interventions or treatments, multi-modal treatment approaches, shared resources across IDDRCs for treatment or assessment, and/or public health approaches to IDDs. Examples of IDDs that the IDDRCs study include chromosomal conditions that cause IDDs, such as Prader-Willi, Angelman, Williams, and Down syndrome, X-chromosome disorders, such as Rett and Fragile X syndromes disorders that involve biochemical processes, and metabolic issues related to brain functioning, such as hypoxia and phenylketonuria. In addition, NINDS continues to support the Morris K. Udall Centers of Excellence in Parkinson's Disease Research Program.[496] Each site serves as a local and national PD research resource, supports career development of early career researchers, and provides pro-active outreach to the local patient/advocacy community.

INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) is an NIH-wide initiative that aims to understand critical health and quality-of-life needs for individuals with Down Syndrome.[497] INCLUDE aims to investigate conditions that affect individuals with Down Syndrome and the general population, such as AD/dementia, autism, cataracts, celiac disease, CHD, and diabetes. Three current priority areas of the initiative are to conduct targeted, high-risk, high-reward basic science studies on chromosome 21, assemble a large study population (cohort) of individuals with Down syndrome, and include individuals with Down syndrome in new and existing clinical trials.

Another NIH-supported consortium, the MarkVCID consortium, is a collection of nine research sites and a coordinating center to develop biomarkers for the small vessel diseases of the brain that lead to vascular cognitive impairment/dementia (VCID).[498] In 2021, the consortium published the first promising results of several different biomarker protocols that are designed to be used in clinical research and, if further

[494] https://card.nih.gov/
[495] https://www.nichd.nih.gov/research/supported/eksiddrc
[496] https://www.ninds.nih.gov/current-research/focus-disorders/focus-parkinsons-disease-research/parkinsons-disease-research-centers-excellence
[497] https://www.nih.gov/include-project
[498] https://markvcid.partners.org/

validated, eventually in clinical practice to help detect VCID in patients.[499,500] The collection of MarkVCID-developed biomarker protocols includes clinical/cognitive, neuroimaging, fluid, and instrumental measurement tests and procedures.

The NIH BRAIN Initiative is supporting the development of innovative technologies aiming to characterize all cell types in the brain, map connected neurons in circuits and systems, and measure and modulate the activity of specific circuits.[501] The BRAIN Initiative implemented a data sharing policy and invested in a data infrastructure to provide the research community with tools to analyze and visualize the BRAIN Initiative's rich data through three components: data archives, data standards, and software for data integration and analysis. Through the BRAIN Initiative, NIH supports the Cell Census Network (BICCN),[502] a collaboration of over 250 scientists at nearly 50 institutions tasked with developing novel technologies to identify and characterize brain cell types, to use those technologies to develop a brain-wide census of cell types, to create an atlas of these cell types for the mouse, monkey, and human brains, and to collate and share their data with the greater neuroscience community. In 2021, BICCN unveiled an atlas of cell types and an anatomical neuronal wiring diagram for the mammalian primary motor cortex, derived from detailed studies of mice, monkeys, and humans.[503,504] The atlas provides a foundation for future research efforts that dive deeper into the structure and function of cells in the mammalian brain. These studies may include efforts to understand how the brain matures and develops, as well as research examining the roles that distinct cell types play in the creation of complex thought and behavior.

Public-private partnerships are another way that NIH facilitates research and resource sharing. DS-Connect® is a web-based health registry that serves as a national health resource for individuals with Down Syndrome and their families, researchers, and healthcare providers.[505,506] DS-Connect® was established by The NIH Down Syndrome Consortium. Since 2011, NICHD has led this public-private collaboration to foster communication and share ideas among the NIH, individuals with Down Syndrome and their families, national organizations interested in Down Syndrome, and pediatric and other organizations. The registry facilitates communication and online resource sharing through a secure, confidential database. With over 5,000 registrants to date, DS-Connect has allowed many researchers to successfully complete recruitment for their studies.

NIH has also facilitated a new area of research through its support of the development of an AI model to facilitate interpretation of results from GWAS. GWAS have uncovered links between certain common variations in the genetic code and features of autism and psychiatric disorders, including schizophrenia,

[499] Wilcock D, et al. *Alzheimers Dement*. 2021 Apr;17(4):704-715PMID: 33480172.
[500] Lu H, et al. *Alzheimers Dement*. 2021 Apr;17(4):716-725. PMID: 33480157.
[501] https://www.braininitiative.nih.gov/
[502] https://braininitiative.nih.gov/research/tools-and-technologies-brain-cells-and-circuits/brain-initiative-cell-census-network
[503] BRAIN Initiative Cell Census Network (BICCN). *Nature*. 2021 Oct;598(7879):86-102. PMID: 34616075.
[504] https://directorsblog.nih.gov/2021/10/14/first-comprehensive-census-of-cell-types-in-brain-area-controlling-movement/
[505] https://dsconnect.nih.gov/
[506] https://downsyndrome.nih.gov/

depression, and eating disorders.[507,508,509,510,511,512,513] To translate genetic associations into causal disease mechanisms, the PsychENCODE Consortium used a large sample of postmortem human brains to develop an AI model that is six times better than previous models at predicting risk for mental disorders.[514] They also pinpointed several hundred previously unknown risk genes for mental illnesses and linked many known risk variants to specific genes. NIMH is also supporting more than 800 investigators from more than 150 institutions in 40+ countries through the Psychiatric Genomics Consortium (PGC). The PGC aims to advance genetic insights of psychiatric disorders through research projects including the largest GWAS of bipolar disorder to date.

Guiding the Field

Neuroscience is an interdisciplinary field. As neuroscience research at NIH is supported by more than 14 different ICs, it is vital that priorities be set together with input from the whole field. One of the ways in which NIH does this is by bringing researchers together to share their findings and discuss future research opportunities. NINDS hosted the 3rd ADRD Research Summit in 2019, a triennial conference for coordinated planning efforts that respond to the National Plan to Address Alzheimer's Disease.[515] The conference set national research recommendations that reflect critical scientific priorities for research on AD and ADRD. NINDS also hosted a virtual conference, Curing the Epilepsies 2021: Setting Research Priorities, to evaluate the current state of epilepsy research and consider priorities for future efforts.[516,517] The conference directly informed the development of Benchmarks for Epilepsy Research, [518] which reflect priorities shared across the epilepsy community for research toward clinically meaningful advances in understanding and treating the epilepsies. This conference was the fourth in a series of Curing the Epilepsies conferences held approximately every seven years since 2000. Additionally, NIA, NIDCD, and NIDDK sponsored the Sensory Nutrition and Disease Workshop in which researchers came together to discuss the pathways linked to tasting and sensing of food, and the physiological roles of chemosensory receptors and how these taste and smell sensors are involved in nutrition.[519]

---

[507] Mullins N, et al. *Nat Genet*. 2021 Jun;53(6):817-829. PMID: 34002096.
[508] Cross-Disorder Group of the Psychiatric Genomics Consortium. *Cell*. 2019 Dec 12;179(7):1469-1482.e11. PMID: 31835028.
[509] Khan TA, et al. *Nat Med*. 2020 Dec;26(12):1888-1898. PMID: 32989314.
[510] Schrode N, et al. *Nat Genet*. 2019 Oct;51(10):1475-1485. PMID: 31548722.
[511] Mukai J, et al. *Neuron*. 2019 Nov 6;104(3):471-487.e12. PMID: 31606247.
[512] Akula N, et al. *Neuropsychopharmacology*. 2021 Jun;46(7):1364-1372. PMID: 33558674.
[513] Watson HJ, et al. *Nat Genet.* 2019 Aug;51(8):1207-1214. PMID: 31308545.
[514] https://www.nimhgenetics.org/resources/psychencode
[515] https://www.ninds.nih.gov/News-Events/Events-Proceedings/Events/Alzheimers-Disease-Related-Dementias-Summit-2019
[516] Marsh ED, et al. *Epilepsy Curr*. 2021 Jun 30;21(5):389-393. PMID: 34924844.
[517] https://www.ninds.nih.gov/news-events/events/curing-epilepsies-2021-conference
[518] https://www.ninds.nih.gov/about-ninds/strategic-plans-evaluations/strategic-plans/2021-aesninds-epilepsy-research-benchmarks
[519] Reed DR, et al. *Am J Clin Nutr*. 2020 Dec 9;113(1):232–45. PMID: 33300030.

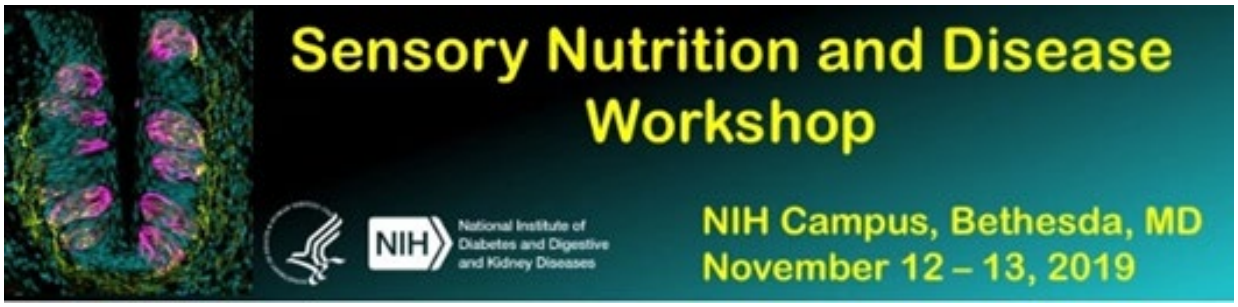


Figure 20: Workshop Banner Taste Papilla. Credit: Dany Gaillard, Ph.D., and Linda Barlow, Ph.D., University of Colorado Anschutz Medical Campus, NIH support from NIDCD

The BRAIN Initiative also engaged in community listening in order to set its priorities for the coming years. In 2019, the "BRAIN 2.0" working group brought together members of the research community through workshops and listening sessions, assessed progress and advances, identified new opportunities, and integrated stakeholder input into their report, "The BRAIN Initiative 2.0: From Cells to Circuits, Toward Cures," as a guide for NIH when considering future priorities and investments.[520,521] The NIH BRAIN Initiative partnered with the Department of Energy (DOE) Office of Science in 2021 to organize and convene five virtual scientific workshops on brain connectivity mapping, which brought together scientists and engineers with broad expertise to discuss challenges and opportunities. The participants prepared a comprehensive report of insights from the workshops that is guiding planning of a BRAIN Initiative transformative project on brain connectivity mapping and potential DOE collaborations. Through these engagements, NIH listens to the research community's priorities and use them to inform how NIH guides the field for the future.

NIH articulates its upcoming priorities through strategic planning. In 2019, NICHD led efforts to publish the *NIH Strategic Plan for Research on FMR1-associated Conditions*, which identifies priorities for NIH research activities on three conditions known to be associated with the *FMR1* gene: Fragile X syndrome, Fragile X-associated Tremor and Ataxia Syndrome, and Fragile X-associated Primary Ovarian Insufficiency. This Plan shapes the work of the Centers for Collaborative Research in Fragile X and FMR1-Associated Conditions and includes support for research to improve the diagnosis and treatment of Fragile X syndrome (FXS) and other conditions associated with mutations in the *FMR1* gene.[522,523] It also describes research directions on the *FMR1* gene itself, mutations that affect the gene's function, and the role of the FMR1 protein in the development and progression of these conditions. The plan was developed over several years and incorporates input from scientists, healthcare providers, and support organizations with an interest in *FMR1*-related conditions, as well as families and individuals affected by the conditions.

NINDS recently published its FY 2021-2026 NINDS Strategic Plan, which presents an overarching strategic framework to accelerate science that will result in improvements in quality of life for all people with

[520] https://brainconnectivityseries.com/
[521] https://braininitiative.nih.gov/vision/nih-brain-initiative-reports/brain-20-report-cells-circuits-toward-cures
[522] https://www.nichd.nih.gov/research/supported/ccrfx
[523] https://www.nichd.nih.gov/publications/product/491

neurological disorders, and ultimately to prevent or cure these diseases.[524] The Institute's guiding vision is a world that is free from suffering due to neurological disorders. NINDS' role is to optimize the taxpayers' investment in neuroscience to maximize the impact and accelerate the pace of discovery. In addition to outlining NINDS scientific goals, the plan includes strategies related to NINDS training and workforce diversity, workforce culture, and communications activities, guiding the field into the future.

Life Stages, Human Development, and Rehabilitation

Research on human development and life stages complement each other by illuminating the intricate dynamics between biological, psychosocial, and environmental factors on our health and well-being, from pre-birth to later in life. NIH research in these areas highlights ICOs' unique foci and expertise as well as the collaborative and complementary nature of their work. Through research and related activities, NIH is actively contributing to a broad evidence base to help inform effective strategies for enhancing health and promoting resilience across the lifespan.

Summary of NIH Activities

NIH funds research in these areas throughout each of the 27 ICs. In particular, the *Eunice Kennedy Shriver* NICHD—which focuses on the needs of children, pregnant individuals, and people with disabilities—and NIEHS—with a mission to discover how the environment affects people in order to promote healthier lives—contribute to this area. NIA has pioneered work on aging that has shed light on the effects of earlier life experiences on health in the aging population. In addition, the Environmental Influences on Child Health Outcomes (ECHO) Program aims to understand and enhance the health of children for generations to come by enabling investigators and the wider community of scientists to address research questions about the effects of a broad range of early environmental exposures on child health and development.[525]

Human Development

NIH research continually reveals the complex interplay between a multitude of genetic and environmental factors in human development. Understanding how this interplay leads to typical and atypical developmental processes can improve our ability to prevent or reduce illness and disability.

How genetic factors and pre-birth exposure to harmful substances affect human development and human health is the focus of the Study of Pregnancy And Neonatal Health (SPAN). Launched by NICHD, SPAN integrates different research approaches to better understand the health consequences of genetic influences and prenatal exposures and how they may impact not just one individual but multiple generations.[526] This multi-site study will recruit a large cohort of pregnant women and their male partners. In addition, the investigators will conduct a sub-study focusing on women with gestational diabetes. SPAN is designed to explore the relationships between the father's cardio-metabolic risk factors and the health of newborns, fetal growth and aging of the placenta, and timing of delivery and newborn deaths, especially in deliveries complicated by gestational diabetes.

[524] https://www.ninds.nih.gov/about-ninds/strategic-plans-evaluations/strategic-plans/ninds-strategic-plan-and-priorities
[525] https://www.nih.gov/echo
[526] https://www.nichd.nih.gov/about/org/dir/dph/officebranch/eb/SPAN

A growing body of research is shedding light on how parental exposure to harmful substances before conception may affect pregnancy and beyond. A recent study, supported by NIEHS, showed that exposure to polybrominated biphenyl (PBB) 153, a type of flame retardant used in foam and plastics, alters DNA methylation in sperm[527] (DNA methylation is one of the biological processes that regulate which genes in our cells are turned on or off). Direct exposure to PBB153 is toxic to living organisms, and this study suggests that it may also harm future generations by affecting specific genes in sperm that are essential for fetal development.

Some chemicals found in personal care products, such as soaps, cosmetics, and toothpaste, are known or suspected to disrupt reproduction, metabolism, and other biological processes. An NIEHS-funded study examined the relationship between pre-birth exposure to such chemicals and the timing of puberty. Girls who were born to mothers with higher levels of two chemicals, diethyl phthalate and triclosan, in their bodies during pregnancy entered puberty at younger ages[528] (this association was not found in boys). The study highlights the importance of understanding how early life exposures may influence the timing of puberty, as early puberty is linked to increased health risks (e.g., breast and ovarian cancer).

Preterm birth happens when a baby is born before 37 weeks of pregnancy have been completed. In 2020, preterm birth affected one of every ten infants born in the U.S.[529] The Neonatal Research Network (NRN) is a collaborative network of neonatal intensive care units across the U.S., comprising 18 clinical centers and a data coordinating center, supported by NICHD with co-funding from other ICs for specific projects.[530] Focused on newborns, particularly extremely low-birth-weight infants, the NRN conducts clinical trials and clinical studies that seek to improve the treatment and health outcomes of critically ill newborns.[531]

Birth defects are structural (how the body is built) or functional (how the body works) abnormalities present at birth that can cause physical disability, intellectual and developmental disorders, and other health problems. The mission of the Birth Defects Initiative (BDI) is to capitalize on genomic and other biomedical discoveries to further understanding of the mechanisms responsible for structural birth defects, which affect about three percent of all live births in the U.S. each year.[532] The initiative supports basic scientists and clinicians whose research projects span basic, translational, and clinical approaches to understanding the developmental biology and genetics of structural birth defects. The ultimate goal of BDI is the development of new, innovative, and valuable strategies for the molecular diagnosis, treatment, and prevention of human structural birth defects.

Children with birth defects have an increased risk of developing childhood cancer, which suggests that there are shared genetic pathways underlying some types of childhood cancer and structural birth defects. The Gabriella Miller Kids First Pediatric Research Program (Kids First) is an NIH-wide program led by

[527] Greeson KW, et al. *Sci Rep.* 2020 May 22;10(1):8567. PMID: 32444626.
[528] Harley KG, et al. *Hum Reprod.* 2019 Jan 1;34(1):109-117. PMID: 30517665.
[529] https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm#
[530] https://neonatal.rti.org/
[531] https://www.nichd.nih.gov/research/supported/nrn
[532] https://www.nichd.nih.gov/research/supported/bdi

NICHD, NCI, NHGRI, and NHLBI, and supported through the NIH Common Fund.[533] It was initiated in response to the *2014 Gabriella Miller Kids First Research Act.*[534] Kids First aims to foster collaborative research to uncover the causes of childhood cancers and structural birth defects (related to a problem with the structure of body parts, such as cleft palates or heart defects), including the discovery of shared genetic pathways between these disorders, and to support data sharing within the pediatric research community. Between 2015 and 2021, the program selected 44 childhood cancers and structural birth defects cohorts for whole genome sequencing, which involved 20,000 children with childhood cancer and structural birth defects and their families. In 2020, using genetic data accessible through the Kids First Data Resource Portal,[535] scientists discovered a new gene region linked to the risk of orofacial clefts (OFCs).[536] OFCs are structural birth defects which occur when a baby's lip or mouth does not form properly during pregnancy and are some of the most common birth defects.

ASD is a complex disorder that begins early in life and affects how a person acts, learns, and interacts with others. Early detection and early intervention can improve the lives of children with ASD. Currently there is no medical test to diagnose ASD, but there is promising research that could advance ASD detection. For example, NIEHS-funded researchers identified patterns in pregnant mothers' autoantibodies that were highly associated with the diagnosis and severity of ASD.[537] Autoantibodies refer to proteins made by a person's immune system that attack the body's own tissues. The researchers applied machine learning to identify, with 100 percent accuracy, patterns specific to maternal autoantibody-related ASD, which accounts for around 20 percent of all autism cases. Based on this study, maternal autoantibodies may be used to aid in the early diagnosis and intervention of maternal autoantibody-related ASD.

Melanocortins are a group of hormones involved in appetite and food intake. A research team, supported by NIDDK and NICHD, identified a type of melanocortin receptor, MC3R, that links childhood nutrition to the timing of puberty and growth.[538] People who carried mutations that disrupted the function of MC3R started puberty later than those who did not have the mutations. In addition, MC3R mutations were linked to shorter height, lower lean body mass, and low levels of a hormone involved in childhood growth. The research team also identified a small number of children with the MC3R mutations and found that all were shorter than average. The results suggest that MC3R plays an important role in influencing puberty and growth.

Technology and social media use among children and teenagers is increasing (especially during the COVID-19 pandemic), making it critical to study how technology affects child development. A new NICHD initiative, Impact of Technology and Digital Media (TDM) Exposure/Usage on Child and Adolescent Development, will fund research projects that examine the pathways by which TDM exposure and usage

[533] https://commonfund.nih.gov/kidsfirst
[534] https://www.govinfo.gov/content/pkg/PLAW-113publ94/html/PLAW-113publ94.htm
[535] https://portal.kidsfirstdrc.org/login
[536] https://commonfund.nih.gov/kidsfirst/highlights
[537] Ramirez-Celis, A et al. Mol Psychiatry. 2021 May;26(5):1551-1560. PMID: 33483694. https://health.ucdavis.edu/news/headlines/biomarkers-in-mothers-plasma-predict-a-type-of-autism-in-offspring-with-100-accuracy/2021/01
[538] Lam BYH, et al. *Nature*. 2021 Nov 3. PMID: 34732894.

impact developmental trajectories and health outcomes in early childhood (ages birth to eight years old) and adolescence (ages 9-17).[539]

Both increased screen time and preterm birth are associated with an increase in risk of developmental and behavioral problems, yet there is limited data on the association of screen time with cognitive and behavior outcomes in children born extremely preterm (before the 28th week of pregnancy). Researchers, supported by NICHD, NHLBI, and NCATS, analyzed data from over 400 children born extremely preterm, and found that many had high screen time use.[540] Fifty-seven percent of the children spent more than two hours per day with screen time and almost two-thirds had a television or computer in their bedroom. High screen time (two hours or more per day) was associated with an increased risk of cognitive, executive function, and behavioral problems at early school age among six- to seven-year-old children after adjusting for other factors. There was also an association of high screen time with overweight, and children with high screen time were more likely to have lower average minutes per day of structured physical activity than children with low screen time.

Life Stages

Our health and health needs change throughout the life course. Therefore, NIH continually seeks to expand the knowledge base on how our bodies grow, age, and change in response to changing circumstances and environment.

The inclusion of scientifically appropriate and relevant populations in NIH-funded clinical research is delineated in NIH's Inclusion Across the Lifespan policy became effective for all grant applications submitted on or after January 25, 2019.[541] The policy requires individuals of all ages be included in clinical studies unless there are scientific or ethical reasons not to include them. The policy aims to ensure that children and older adults are not inappropriately excluded from clinical studies.[542] Insights garnered from this expanded inclusion approach could enhance reproducibility and generalizability of clinical study findings, further strengthening the foundation that informs clinical practices and public policies.

Reproductive Health and Preconception

Reproductive health includes preconception health and health care, which focus on actions parents can do before and between pregnancies to increase the chances of having a healthy baby. In 2021, the ECHO Program collaborated with NCI, NIAID, NICHD, NIEHS, and OBSSR to host the Preconceptional Origins of Child Health Outcomes Workshop.[543] Experts from many scientific disciplines (e.g., human embryology, immunology, epidemiology, biostatistics, psychology, medicine, nutrition, health disparities) were invited to discuss the state of the science, identify research gaps, and scientific opportunities focusing on how preconception exposures may influence child health outcomes. In addition, the workshop addressed how to overcome operational challenges in conducting preconception cohort studies. As a result of the workshop, the ECHO Program will include a preconception pilot study in its next phase scheduled to begin

[539] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-22-009.html
[540] Vohr, BE, et al. *JAMA Pediatrics.*2021. PMID: 34251406.
[541] https://grants.nih.gov/policy/inclusion/lifespan.htm
[542] Bernard MA, et al. *JAMA*. 2018;320(15):1535–1536. PMID: 30326521.
[543] https://echochildren.org/preconceptional-origins-of-child-health-outcomes/

in FY 2023.[544] The pilot study will enroll about 10,000 preconception women and their partners, which is expected to lead to about 3,000 births. The pilot study will provide valuable insights how factors in the preconception period (e.g., lifestyle, physical and chemical exposure, psychosocial variables) are related to child health outcomes.

It is increasingly clear that lifelong health and well-being begin before birth. NIH supports research on all aspects of reproductive health, including pregnancy, contraception, and fertility/infertility. In a recent study of mice, which share similar genes with those in humans[545], NIEHS scientists found that DNA methylation patterns were closely linked to the genetic makeup of the animal. These patterns were unchanged when passed to male and female offspring. However, in female animals that had experienced pregnancy, hundreds of DNA sites showed decreased methylation, which was not found in virgin females. Their findings suggest that DNA sequence may determine where methylation events occur, and that life events, such as pregnancy, could alter DNA methylation patterns.

The development of safe and effective contraceptive methods for men has been an ongoing quest for scientists. A better understanding of male reproductive physiology is limited by incomplete information on the genes that are expressed in reproductive tissues. NICHD-supported researchers analyzed publicly available datasets of human and mouse ribonucleic acid (RNA), which plays a central role in turning genetic information into proteins that determine cell function, as well as newly acquired human and mouse tissue samples from reproductive organs, in order to identify genes that appear only or primarily in the reproductive tract.[546] They detected 1,178 genes that were identified for the first time as potentially specific to the reproductive tract. Further analysis showed that 51 of those genes were specific to the male reproductive tract, but no mouse models had been developed for studying the function of those genes. The researchers subsequently engineered mouse models for six genes, and three were found to be associated with infertility in mice. These genes provide insight into reproductive processes, as well as could serve as potential targets for the development of male contraceptives.

To advance reproductive health research and its translation into practice, NICHD's National Centers for Translational Research in Reproduction and Infertility (NCTRI) form a national network of centers that promote multidisciplinary interactions between basic and clinical scientists interested in establishing high-quality translational research programs in the reproductive sciences. The centers also serve as national resources for the training and career development of young scientists electing to pursue careers conducting research in high-priority areas of reproduction and infertility. The centers facilitate and accelerate bidirectional knowledge transfer between the laboratory and clinic, with the goal of improving human reproductive health through enhanced communication, innovation, and research excellence.

Infancy to Adolescence

Infants and children living in rural areas and states are less likely than those living in other states to have a chance to enroll in clinical research, especially clinical trials. To address this issue, the ECHO Program

[544] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-171.html
[545] https://www.genome.gov/10001345/importance-of-mouse-genome
[546] Robertson MJ, et al. *BMC Biol.* 2020 Aug 19;18(1):103. PMID: 32814578.

partnered with the Institutional Development Award (IDeA) program[547], managed by NIGMS, to establish the IDeA States Pediatric Clinical Trials Network (ISPCTN). ISPCTN has research sites in 18 states. It seeks to reduce disparities in pediatric research by providing medically underserved and rural populations with access to state-of-the-art pediatric clinical trials and by building pediatric research capacity in states with historically limited NIH funding.

NICHD leads a variety of efforts to study and promote child health and well-being. The Institute's Newborn Screening Translational Research Network provides resources and infrastructure for researchers studying newborn screening.[548] Newborn screening can detect disabling or potentially fatal conditions in newborns, often before the infant displays any signs or symptoms of a disease or condition. Since newborn screening programs began in the 1960s, more than 150 million infants have been screened for genetic and congenital disorders.[549] Recent newborn screening developments include: a diagnostic assay that allows faster and cheaper newborn screening for cystic fibrosis, a bile-based newborn screen for Niemann-Pick disease type C, biomarkers for the rare genetic disorder medium chain acyl-coA dehydrogenase deficiency (MCADD)) in newborn blood spots, quicker diagnosis of propionic acidemia, and FDA approval for a device that can detect lysosomal storage disorders. Recent advances have used AI analysis methods, including natural language processing, to accelerate genetic diagnosis of rare disorders.

NICHD also supports research on sudden infant death syndrome (SIDS), the leading cause of death in children between one month and one year of age.[550] In addition, NICHD partners with other agencies and private organizations to disseminate information about safe sleep environments to reduce the risk of SIDS and other sleep-related causes of infant death. The Safe to Sleep® campaign offers printable and sharable resources accessible on the internet, including information tailored to specific audiences.[551] The campaign relies on trusted community members to act as intermediaries, sharing safe sleep information with parents and caregivers who come to them for care, services, or information. These intermediaries (health care providers, community health workers, tribal leaders and elders, and leaders of community organizations) help to further the campaign's reach by sharing safe sleep messages with their patients, clients, and others in the community.

NICHD also has a long-standing interest in learning disabilities. The Institute established the Learning Disabilities Research Centers (LDRC) Consortium to understand the causes, origins, and developmental course of learning disabilities.[552] The LDRC Consortium studies learning disabilities that affect reading and writing, including basic reading skills, reading fluency, reading comprehension, and written expression. Complementing the LDRC Consortium, the Learning Disabilities Innovation Hubs focus on understudied

[547] https://www.nigms.nih.gov/Research/DRCB/IDeA/Pages/default.aspx
[548] https://nbstrn.org/
[549] Newborn Screening: Toward A Uniform Screening Panel and System at HRSA, 2002. Available at: https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/newborn-uniform-screening-panel.pdf
[550] https://safetosleep.nichd.nih.gov/safesleepbasics/SIDS/fastfacts
[551] https://safetosleep.nichd.nih.gov/
[552] https://www.nichd.nih.gov/research/supported/ldrc

research topics and on projects that study people diagnosed with and at risk for learning disabilities.[553] Projects also include mentorship of researchers who are in the early stages of their careers, with a particular focus on recruiting participants from underrepresented groups in scientific careers.

NIEHS also seeks to create a strong network of healthcare professionals who possess the skills and knowledge to address the complexities of pediatric and reproductive environmental health by launching the Pediatric and Reproductive Environmental Health Scholars program. The program will introduce pediatric healthcare providers, obstetricians/gynecologists, and other interested healthcare professionals to issues in environmental health. Participants will gain research experiences that bridge clinical practice in environmental health, community-level engagement, and teaching.

Home visiting by a trained professional (such as a nurse, social worker, or early childhood specialist) during pregnancy and early childhood has been shown to improve maternal, child, and family outcomes.[554] A recent NICHD-supported study added to the evidence base by showing that a program that provides new parents with one to three home visits from a nurse soon after a child's birth was associated with 39 percent fewer child protective service investigations for maltreatment through age five, compared to parents who received usual newborn services.[555] Families receiving the visits also had 33 percent fewer emergency department visits. The visiting nurse program features instruction for parents on how to feed infants, manage infant crying, and other aspects of infant health. Nurses also screen parents' mental health and availability of social and emotional support. Collectively, the study results suggest that a program of brief nurse home visits soon after birth can have benefits into early childhood, reducing rates of child maltreatment and use of emergency medical care.

NICHD established the CAPSTONE Centers for Multidisciplinary Research in Child Abuse and Neglect to address child maltreatment as a significant public health concern.[556] These specialized centers conduct research to assess the efficacy and effectiveness trials of child abuse and neglect interventions, examine the long-term impact of specific and understudied types of maltreatment, study the neurobiology of abuse and neglect and implications for health outcomes, and develop screening tools and assessment measures for early identification and treatment of specific types of abuse and neglect. The centers' focus on multidisciplinary projects will provide opportunities for community members, students, and faculty at all levels to be exposed to cutting-edge educational tools and technologies, research, and clinical expertise within the field of child maltreatment.

Adulthood to Middle Age

Life expectancy, the average number of years a newborn can expect to live, increased by almost ten years between 1959 and 2016 in the U.S., from 69.9 years to 78.9 years. However, it declined for three consecutive years after 2014, driven largely by a higher mortality rate in people ages 25-64 across all racial groups. NIA-supported investigators found that major causes of the higher mortality rate were drug

[553] https://www.nichd.nih.gov/research/supported/ldhubs
[554] https://nhvrc.org/about-home-visiting/why-home-visiting/
[555] Goodman, WB, et al. *JAMA Netw Open*. 2021;4(7):e2116024. PMID: 34232300.
[556] https://www.nichd.nih.gov/research/supported/CAPSTONE

overdoses, alcohol-related liver disease, and suicide.[557] Potential explanations for this troubling trend include the opioid epidemic, tobacco use, obesity (which is associated with numerous health disorders), deficiencies in the health care system that disproportionately affect people in middle age, increased levels of psychological distress, and socioeconomic stressors such as financial insecurity. To better understand why Americans in the prime of life are dying at an increased rate than in years past, NIA supported a 2021 report, conducted by the National Academies of Science, Engineering, and Medicine (NASEM) entitled *High and Rising Mortality Rates Among Working-Age Adults*,[558] as well as two funding opportunity announcements,[559,560] to create opportunities for studying what factors underlie the rising death rate of young and middle-aged adults in the U.S.

Unhealthful behaviors, such as smoking, drug and alcohol abuse, overeating, and a sedentary lifestyle, contribute to negative health outcomes and common diseases. There are few effective approaches to adopting and maintaining healthy behaviors. The Science of Behavior Change (SOBC) program, established by the NIH Common Fund in partnership with 17 ICOs, brought together scientists from various disciplines, spanning basic and translational science across different health-related behaviors, to explore how a focus on the mechanisms of behavior change in the development of behavior change interventions could reliably improve health outcomes. Research funded during the first stage of the program led to the identification of three broad classes of intervention targets that are highly relevant to understanding the mechanisms of behavior change: self-regulation, stress reactivity and stress resilience, and interpersonal and social processes.[561] In the second stage of the program, a network of SOBC researchers identified potential targets for behavior change interventions and demonstrated that these targets were promising as drivers of behavior change, measurable in multiple ways, and relevant to various diseases and conditions like type 2 diabetes, and chronic pain.[562] The end of the SOBC program was marked by the SOBC Capstone Conference that highlighted research along the behavior change intervention development pipeline, identified opportunities for future research, and highlighted synergies between SOBC and related initiatives.[563]

Many people seek out complementary health approaches, such as using non-mainstream health practices including dietary supplements, acupuncture, or spinal manipulation, together with conventional medicine to improve or maintain their health. Recently, NCCIH researchers addressed gaps in the study of complementary health approach by completing the first longitudinal analysis of the use of complementary health approach in a nationally representative sample of adults in the U.S.[564,565] The analysis identifies

[557] https://www.nia.nih.gov/news/deaths-middle-aged-adults-drive-decrease-u-s-life-expectancy
[558] National Academies of Sciences, Engineering, and Medicine. 2021. *High and Rising Mortality Rates Among Working-Age Adults*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25976.
[559] https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-23-004.html
[560] https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-22-025.html
[561] https://commonfund.nih.gov/behaviorchange
[562] https://www.nia.nih.gov/research/blog/2020/09/celebrating-successes-and-next-steps-science-behavior-change-program
[563] https://commonfund.nih.gov/sobc-capstonemeeting
[564] Scott R, et al. *J Altern Complement Med* 2021 Jul;27(7):550-568. PMID: 33877882.
[565] https://www.nccih.nih.gov/research/research-results/first-longitudinal-analysis-of-complementary-health-approach-use-by-us-adults-identifies-factors-that-predict-new-continued-and-discontinued-use

factors associated with use of four common complementary approaches (massage therapy, meditation, chiropractic, and herbal products) over nearly two decades and how they are related to starting, continuing, or stopping an approach. Factors such as age, sex, and education were associated differently with new and continued use of complementary health approaches, with prior use of each approach having the most significant relationship with future use. Additional research is needed to confirm the findings and to investigate other important populations, such as veterans, in which there are significant gender, race, and ethnicity differences among those who use complementary health approaches. Nonetheless, this longitudinal analysis is a promising step towards developing the baseline knowledge for education and outreach efforts to patients, providers, and health plans.

There is growing evidence that calorie restriction (reducing daily caloric intake while meeting nutritional needs) results in improvement in a variety of health conditions in animals and in humans. In a recent study of non-obese adults under age 50, an average 12 percent reduction in caloric intake over two years substantially reduced waist measurements, blood pressure, low-density lipoprotein (LDL) cholesterol, and triglycerides, while measures of inflammation, insulin resistance, glucose control, and metabolic syndrome greatly improved.[566] Calorie restriction also extends lifespan for many animal species, though there is no current evidence to confirm this happens in people. NIA-supported investigators are working to identify the biological pathways through which calorie restriction exerts its potentially beneficial effects.[567] In addition, they are exploring the development of calorie restriction mimetics (compounds that target the same pathways affected by calorie restriction) with the goal of finding ways to extend human lifespan. Compounds such as resveratrol, rapamycin, and metformin have shown promise in animal studies, although the effectiveness of these treatments in humans remains less clear. Calorie restriction mimetics are one type of compound in which investigators in the NIA-supported Interventions Testing Program (ITP) have taken a keen interest.[568] Since 2003, the ITP, a multi-institution study of compounds with the potential to delay disease and dysfunction in a mouse model of aging, has tested potential interventions including foods, diets, drugs, and hormones. To date, seven compounds have been found to extend lifespan in female and male mice.

(NAFLD involves the buildup of excessive fat in the liver of an individual who is not a heavy consumer of alcohol, increasing the risk of liver damage. NAFLD is now the most common liver disorder in the Western countries.[569] Experts estimate that about 24 percent of U.S. adults have NAFLD. To examine how diet affects the liver, NIEHS scientists fed mice a high-fat diet, which caused the mice to become obese and showed other changes similar to metabolic syndrome in humans (metabolic syndrome refers to a group of conditions that raises a person's risk for heart disease, diabetes, and other serious health problems). Moreover, their livers became fatty and showed wide-ranging abnormalities at both molecular and cellular levels. The researchers determined that when too many calories are consumed, the mouse liver

[566] Kraus WE et al. *Lancet Diabetes Endocrinol*. 2019 Sep;7(9):673-683. PMID: 31303390.
[567] https://www.nia.nih.gov/news/live-long-good-health-could-calorie-restriction-mimetics-hold-key
[568] https://www.nia.nih.gov/research/dab/interventions-testing-program-itp
[569] https://medlineplus.gov/genetics/condition/non-alcoholic-fatty-liver-disease/#frequency

adapts by reprogramming the regulation of gene activity.[570] These insights into how the liver adapts to a high-fat diet may lead to novel treatments for NAFLD and other obesity-related diseases.

Through basic, translational, and clinical research, the National Center for Medical Rehabilitation Research (NCMRR), a component of NICHD, aims to develop scientific knowledge needed to enhance the health, productivity, independence, and quality of life of people with physical disabilities.[571] NCMRR funds a range of research in rehabilitation medicine to advance patient care. In FY 2021, one research team supported by NCMRR demonstrated that high doses of concentrated constraint-induced movement therapy, which is designed to improve arm and hand function, produced several lasting benefits for children with cerebral palsy.[572] Another NCMRR-funded research team developed a biomedical interface that connects existing muscles and neurons to improve function for prosthetic limbs.[573]

NIEHS leads efforts to expand our understanding of how environmental factors may contribute to disease and disability. NIEHS' Division of the National Toxicology Program (DNTP) conducts innovative toxicology research that reflects real-world public health needs and translates scientific evidence into knowledge that can inform individual and public decision-making. In 2021, the Division released a strategic framework for organizing and implementing its research portfolio, which includes issues ranging from cardiovascular health and developmental neurotoxicity to occupational exposures and scientific cyberinfrastructure.[574]

In 2021, NIEHS hosted the Workshop on Extracellular Vesicles, Exosomes, and Cell-cell Signaling in Response to Environmental Stress.[575] Extracellular vesicles (EVs) play an important role in communication between cells and between organs. EVs have been linked to various biological processes in both normal and disease states. There is growing interest in understanding how EVs may help scientists identify early signs of disease caused by environmental exposures. The workshop provided a platform for participants to discuss the state of the science and technology with respect to the role of EVs and cell signaling in response to environmental stress, and to identify research gaps and scientific opportunities for integrating EVs into environmental health research.

In 2020, NIEHS sponsored the Integrating the Science of Aging and Environmental Health Research: A Workshop, which explored emerging research at the intersection between aging, longevity, environmental exposures, and human health.[576] Scientists have known that environment plays an important role in aging. Research has shown that human exposure to environmental pollutants can exacerbate age-related diseases, such as Alzheimer's and Parkinson's disease.[577] However, many questions remain about the mechanisms through which environmental stressors influence aging,

[570] Qin Y et al. *Nat Commun* 2020 Feb 19;11(1):962. PMID: 32075973.
[571] https://www.nichd.nih.gov/about/org/ncmrr
[572] Ramey SL, et al. *Pediatrics* 2021;148 (5): e2020033878. https://doi.org/10.1542/peds.2020-033878
[573] Srinivasan SS, et al. *Proc Natl Acad Sci U S A.* 2021 Mar 2;118(9):e2019555118. PMID: 33593940.
[574] https://www.niehs.nih.gov/research/atniehs/dntp/strategic-plan/index.cfm
[575] https://www.niehs.nih.gov/news/events/pastmtg/2021/extracellular-vesicles/index.cfm
[576] https://www.nationalacademies.org/event/04-07-2020/integrating-the-science-of-aging-and-environmental-health-research-a-workshop
[577] Chin-Chan M, et al. *Front Cell Neurosci*. 2015; 9: 124. PMID: 25914621.

longevity, and the origin of age-related disease. At the workshop, speakers detailed emerging research findings through two lenses: how environmental exposures influence or mediate aging, and how aging influences environmentally-mediated health outcomes. Participants also explored research opportunities and needs, enabling technologies and analytical tools, and mechanisms to anticipate and use new data to inform decisions about personal health choices, public health, medical practice, and environmental regulation.

Old Age

As extreme weather and disaster events are increasing in frequency and severity, older adults, particularly older members of underserved populations, may be particularly vulnerable during and following these events. It is not clear why, but physical and cognitive health, residential context (e.g., community-dwelling versus living in a nursing home or assisted living), and social connectedness represent potential pathways to disproportionate effects in older adults. In 2019, NIA, in partnership with NIEHS and OBSSR, issued two solicitations aimed at stimulating research to explore the impacts of extreme weather and disaster events on the basic biology of aging as well as how extreme weather and disaster events affect older adults.[578,579] The goal is to improve the health and well-being of older adults via increased knowledge about extreme weather and disaster preparedness, response, and recovery.

NIA is the central hub for research on the health and well-being of older adults. The Institute supports a variety of longitudinal studies, harmonization projects, archives, and repositories to facilitate research on aging in the behavioral and social sciences.[580] Data from these studies are available to qualified researchers, subject only to restrictions imposed for some linked administrative data. The Health and Retirement Study (HRS), which surveys a representative sample of over 20,000 people in America aged 50 and older, is NIA's flagship longitudinal study.[581] The HRS provides a wealth of data about aging in America. In addition, countries around the world have fielded their own versions of the HRS,[582] all of which have been harmonized to facilitate cross-national comparisons. The National Health and Aging Trends Study and the National Study of Caregiving are nationally representative data resources for research on late-life disability and caregiving.[583] Recently, NIA established the Health and Aging Data (HaAD) Enclave, a secure cloud-based platform for NIA-funded investigators to conduct analyses using data from NIA-sponsored studies that are linked to Medicare and Medicaid claims data.[584] Enhancing NIA's portfolio of data infrastructure investments is critical in meeting evolving scientific needs to further understand the process and outcomes of aging.

One area of growing concern for older people is polypharmacy—the use of multiple drugs to treat diseases and other health conditions. Polypharmacy is becoming common in older adults, many of whom have multiple chronic conditions. However, managing multiple medications can be complicated and

[578] https://grants.nih.gov/grants/guide/pa-files/PAR-19-249.html
[579] https://grants.nih.gov/grants/guide/pa-files/PAR-19-250.html
[580] https://www.nia.nih.gov/research/dbsr/data-resources-behavioral-and-social-research-aging
[581] https://hrsonline.isr.umich.edu/
[582] https://hrs.isr.umich.edu/about/international-family-studies
[583] https://www.nhats.org/researcher
[584] https://www.nia.nih.gov/research/blog/2022/02/streamlined-secure-access-cms-study-data

expensive, and the use of multiple medications can increase the risk for adverse reactions and drug interactions. The U.S. Deprescribing Research Network, funded by NIA, is building an interdisciplinary community of physicians, pharmacists, nurses, and older adults and their care partners who are interested in improving research in the relatively new field of deprescribing.[585] Deprescribing refers to reducing or stopping medications that are potentially inappropriate or unnecessary. The network's goal is to develop and share resources and support innovative pilot studies to improve the quality of care and health outcomes for older adults.

Dementia care is a longstanding focus of NIA. In 2020, NIA, in conjunction with HHS, hosted the second National Research Summit on Care, Services, and Supports for Persons with Dementia and Their Caregivers.[586] The goal of the summit was to bring together individuals with a variety of backgrounds to identify evidence-based programs, strategies, approaches, and other research that can be used to improve the care, services, and supports of persons with dementia and their caregivers. The resulting research gaps and opportunities synthesized the individual contributions of people living with a disability, care partners, researchers, and other stakeholders involved in the summit process regarding the most critical areas of dementia care research. In addition, NIA partnered with AHRQ and NASEM to assess the evidence for care interventions for persons living with AD and related dementias. The AHRQ review, *Care Interventions for People Living With Dementia and Their Caregivers*,[587] and the accompanying NASEM consensus study report, *Meeting the Challenge of Caring for Persons Living With Dementia and Their Care Partners and Caregivers*,[588] identified opportunities to improve and strengthen the dementia care research base.

A recent effort by NIA to enhance dementia care research is the Imbedded Pragmatic Alzheimer's disease and AD-Related Dementias Clinical Trials (IMPACT) Collaboratory, a nationwide infrastructure to build the nation's capacity to conduct pragmatic clinical trials of interventions embedded within health care systems for people living with dementia and their care partners.[589] Pragmatic trials are different from traditional clinical trials in that they take place at the site of care and are designed to provide real world evidence on the benefits and risks of treatment options for health care providers and patients. Members of the Collaboratory develop and disseminate effective research methods, support the design and conduct of pragmatic trials, including pilot studies, train the next generation of investigators in dementia care, and encourage collaboration among stakeholders, healthcare providers, and investigators. The research supported by the Collaboratory includes culturally tailored interventions and participants from diverse and underrepresented backgrounds.

[585] https://deprescribingresearch.org/
[586] https://www.nia.nih.gov/2020-dementia-care-summit
[587] https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-231-dementia-interventions-final_0.pdf
[588] National Academies of Sciences, Engineering, and Medicine. 2021. *Meeting the challenge of caring for persons living with dementia and their care partners and caregivers: A way forward.* Washington, DC: The National Academies Press. https://doi.org/10.17226/26026.
[589] https://impactcollaboratory.org/

For more information on research on better ways to maintain or restore independence in older adults, please see the Claude D. Pepper Older Americans Independence Centers section in Chapter 4 of this report.

Understanding and Preserving Health Across All Life Stages

Increasingly, climate change is recognized as a source of risk factors to human health, which could exacerbate existing health threats and create new public health challenges. The NIH Climate Change and Health Initiative is a cross-cutting NIH effort to reduce health threats from climate change across the lifespan and build health resilience in individuals, communities, and nations around the world, especially among those at highest risk. An NIH-wide work group on Climate Change and Health Work Group was formed in 2021 with participation from NIEHS, FIC, NIMHD, NIMH, NINR, NICHD, and NHLBI to develop a strategic framework to guide its research investments in the near term and inform the planning of such investments over the long term. NIH released *The NIH Climate Change and Health Initiative Strategic Framework* in February 2022, with extensive input and coordination with community organizations and academic scientists to collect, analyze, and synthesize a diversity of views, needs, and opportunities.[590]

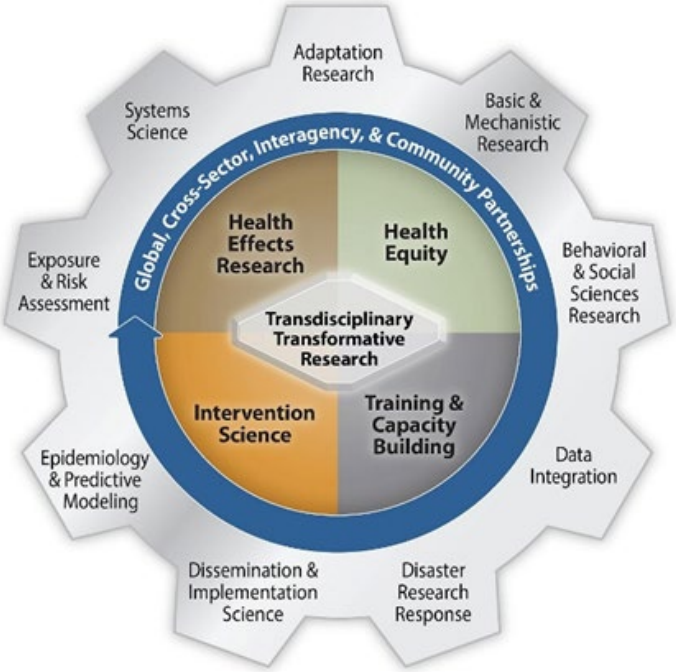


Figure 21: Major themes and program elements of the NIH Climate Change and Health Initiative. Credit: NIH

To advance our knowledge base of how harmful substances in our evolving environment affect health and disease throughout the lifespan, NIEHS, NCI, NHLBI, and the ECHO Program established the Human Health Exposure Analysis Resource (HHEAR). This resource enables NIH-funded researchers to measure environmental exposures and integrate their data with other datasets by providing access to laboratory,

[590] https://www.nih.gov/climateandhealth

statistical, and data science analysis services.[591,592] HHEAR's processes, features, and tools include all life stages and analysis of biospecimens and environmental samples. It serves as a model for incorporating environmental exposure into human health research more rapidly and inexpensively.

The NIH Common Fund invests in short-term programs that are designed to generate deliverables that will catalyze research across multiple biomedical research disciplines. Several of its programs have direct relevance to the study of health and health needs across the lifespan. The recently launched the Cellular Senescence Network (SenNet) program,[593] a collaboration between the NIH Common Fund, NIA, and NCI, will study senescent cells, a type of cells that no longer divide but remain active in the body.[594] These cells play both positive and negative roles in human health. A better understanding of how they affect the body will help researchers develop therapies that encourage beneficial effects of senescent cells while suppressing their damaging effects. The program will identify and characterize differences in senescent cells across the body and lifespan, as well as develop data resources, tools, and technologies for the study of senescent cells.

The Molecular Transducers of Physical Activity Consortium (MoTrPAC), another NIH Common Fund program co-led by NIAMS, NIA, and NIDDK, aims to determine, at the molecular level, how exercise improves and maintains the health of the body's tissues and organs.[595] In 2020, the consortium published a paper outlining their approach to one of the largest research studies of its kind, examining the link between exercise and human health.[596] MoTrPAC aims to assemble a comprehensive map of the molecular changes that occur in response to exercise and, when possible, relate these changes to the benefits of physical activity. MoTrPAC is also developing a user-friendly database that any researcher can access to develop hypotheses for additional studies regarding the mechanisms by which physical activity improves and/or preserves health.

The Knockout Mouse Phenotyping Program (KOMP2), also supported by the NIH Common Fund and led by NHGRI, helps scientists explain the genetic basis of many different types of diseases that occur in both mice and humans.[597] Recently, KOMP2 researchers used machine learning to examine data from mice whose genes were systematically disrupted, or "knocked-out," to determine their function. They found genes potentially associated with altered patterns of activity or food intake, giving new insight into genes involved in circadian rhythm (our natural sleep-wake cycle).[598] The process by which this rhythm gets in synch with regular daylight and dark cycles is not understood. This discovery provided the foundation for a larger and more comprehensive study of circadian behavior to uncover even more genes that help control circadian rhythm and its effects on health and disease.

---

[591] https://www.niehs.nih.gov/research/supported/exposure/hhear/index.cfm
[592] Viet et al. *Int J Hyg Environ Health* 2021 Jun;235:113768. PMID: 34034040.
[593] https://commonfund.nih.gov/senescence
[594] https://www.nih.gov/news-events/news-releases/nih-launches-program-map-rare-type-non-dividing-cells-implicated-human-health-disease
[595] https://commonfund.nih.gov/MolecularTransducers
[596] Sanford JA et al. *Cell* 2020 Jun 25;181(7):1464-1474. PMID: 32589957.
[597] https://commonfund.nih.gov/KOMP2
[598] Zhang T, et al. *PLoS Genet* 2020 Jan 13;16(1):e1008577. PMID: 31929527.

Recently, NHGRI launched a new program that focuses on the regions of the human genome that do not code for proteins (non-coding DNA). DNA contains instructions (coding) that are used to create proteins in cells, but not all DNA sequences code for a protein. The proportion of coding versus noncoding DNA varies significantly between species. In the human genome, almost all (about 98 percent) of the DNA is non-coding. Scientists have learned that some non-coding DNA sequences have functional roles (e.g., regulating which genes are turned on or off), but other areas of non-coding DNA have no known function. This new program, Molecular Phenotypes of Null Alleles in Cells (MorPhiC), aims to develop a consistent catalog describing the form and function of non-coding elements for every human gene. The catalog will be made available for broad use by the biomedical community. Systematically obtaining information about what happens at the molecular and cellular level when specific genes are deleted would provide wide-ranging insights into their biological function. This data would provide a foundation for a better understanding of the mechanisms of action of genes and would help elucidate the roles and relationships of genes and regulatory elements in pathways and networks.

While it is long recognized that the social environment can influence the risk, manifestation, and trajectory of disease and associated symptoms, the underlying biological mechanisms remain understudied. In 2020, NINR partnered with other ICOs to host the *Genomic Response to the Social Environment: Implications for Health Outcomes* workshop, which examined this research area.[599] The transdisciplinary workshop provided a platform to address the relationship among genomics (the study of the complete set of DNA, including all of its genes, in a person or other organism), social environmental factors, and health outcomes. Researchers presented on a diverse set of topics that crosscut diseases, populations, and the lifespan. The workshop stimulated ideas for advancing a social genomics research strategy to illuminate genetic influences on disease burden and to inform future interventions.

Chronic Diseases and Organ Systems

A chronic disease is 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. and the largest contributor towards the nation's $4.1 trillion in annual health care costs.[600] Over half (approximately 52 percent, or 129 million) of all Americans are affected by at least one chronic disease, and the number is growing.[601] In the U.S., six in ten adults have a chronic disease, and four in ten adults have two or more.[602] There are many different categories of chronic disease. Some are fatal: six of the top ten causes of death in the U.S. involved chronic diseases,[603] and 12.6 percent (around 40.6 million) of Americans are disabled or have had their activities limited because of chronic diseases.[604] Furthermore, a 2018 analysis found that treatment of the seven most common chronic diseases, coupled with productivity losses, will cost the U.S. economy $1.1 trillion dollars annually.

[599] https://www.ninr.nih.gov/sites/files/docs/NINR%20Social%20Genomics%20Workshop%20Summary_508c.pdf
[600] https://www.cdc.gov/chronicdisease/about/costs/index.htm
[601] Boersma P et al. Prevalence of Multiple Chronic Conditions Among US Adults, 2018. Prev Chronic Dis 2020;17:200130. https://www.cdc.gov/pcd/issues/2020/20_0130.htm
[602] https://www.cdc.gov/chronicdisease/about/index.htm.
[603] https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.
[604] https://www.census.gov/newsroom/facts-for-features/2020/disabilities-act.html.

However, modest reductions in unhealthy behaviors could prevent or delay 40 million cases of chronic illness per year.[605,606]

Behavioral and environmental factors are two elements that contribute to the onset and development of chronic diseases. Behavioral factors include substance use (e.g., tobacco, excessive alcohol, other drugs), physical inactivity, and poor eating habits, and environmental factors include exposure to toxins, pollutants, and other external factors, particularly for individuals with a higher genetic risk of disease. These long-term diseases affect people of all ages, race, and ethnic groups. Furthermore, age plays a factor in the development and worsening of such chronic conditions as hearing loss, chronic kidney disease, vision loss, and osteoarthritis. Genetics, which can cause chronic diseases at birth (e.g., sickle cell anemia, hemophilia) and throughout development (e.g., asthma, allergies), also play a role. NIH's long-term efforts to better understand, treat, and prevent chronic diseases are helping to reduce the burden of these diseases and conditions.

Summary of NIH Activities

Nearly all NIH ICs support research on chronic diseases. NIH provides crucial support in the area of chronic disease research, from understanding the molecular and cellular mechanisms responsible for human health to clinical applications and behavioral interventions to improve quality of life and reduce disease burden. This section highlights some of the key areas in which NIH is conducting and supporting this research.

Appendix I includes NIH funding for different chronic diseases and organ systems in FY 2019, 2020, and 2021.

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. Common examples include pet dander, pollen, dust, and certain medicines and foods. 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 2018, 19.2 million adults in the U.S. were diagnosed with hay fever, the common term for seasonal allergies, like those caused by pollen.[607] NIH supports allergy research, ranging from basic research in specific allergy and immunology domains, to epidemiological and observational studies to identify risk factors, and clinical trials that are testing new treatment and prevention strategies for different allergies. Below are some examples of current NIH efforts, all led by NIAID.

Understanding Prevalence, Risk Factors, and Underlying Biology

Scientists found that atopic dermatitis, a common inflammatory skin condition also known as allergic eczema characterized by dry, itchy skin, affects nearly 20 percent of children, 30 percent of whom also

[605] Warers H and Graf M. The Costs of Chronic Disease In The U.S. Milken Institute. August 2018. https://milkeninstitute.org/sites/default/files/reports-pdf/ChronicDiseases-HighRes-FINAL_0.pdf.
[606] Raghupathi W and Raghupathi V. *Int J Environ Res Public Health*. 2018 Mar; 15(3): 431. PMID: 29494555.
[607] https://www.cdc.gov/nchs/fastats/allergies.htm

develop food allergies. Scientists have found that the skin rash of children with both atopic dermatitis and food allergy was indistinguishable from the skin rash of children with atopic dermatitis alone. However, there were significant differences in the structure and molecular composition of the top layer of non-lesional, healthy-appearing skin between children with atopic dermatitis and food allergy compared with children with atopic dermatitis alone. Defining these differences may help identify children at elevated risk for developing food allergies.[608,609]

Moisturizing skin at least twice a day with creams, ointments, or lotions to seal in moisture and prevent water loss can help prevent or lessen the symptoms of atopic dermatitis, commonly known as eczema. New NIAID-funded research co-funded by NCATS delineates how two relatively common variations in the *KIF3A* gene are responsible for an impaired skin barrier that allows increased water loss from the skin, promoting the development of atopic dermatitis. This finding could lead to genetic tests that empower parents and physicians to take steps to potentially protect vulnerable infants from developing atopic dermatitis and additional allergic diseases.[610,611]

NIAID-funded researchers discovered that scratching the skin can trigger a series of immune responses culminating in an increased number of activated mast cells (immune cells involved in allergic reactions) in the small intestine. This newly identified skin-gut communication helps illuminate the relationship between food allergy and atopic dermatitis. Researchers studying mice found that some cells in the skin respond to scratching (simulated by applying and removing small strips of tape on the skin) by releasing a signaling protein that travels to the gut and, in concert with other proteins, causes the expansion of intestinal mast cells. Notably, mice that underwent tape stripping had more severe reactions to food allergen than mice that did not. Although additional work is needed to determine the relevance of the findings to humans, the researchers suggest that interventions to limit itching potentially could lessen the severity of food allergy among people with atopic dermatitis.[612,613]

Researchers have identified a subtype of immune cell that drives the production of antibodies associated with anaphylaxis and other allergic reactions. This subset of T cells, T follicular helper cell 13 (Tfh13 cells), were discovered in laboratory mice bred to have a rare genetic immune disease that in humans leads to recurrent viral infections of the skin and respiratory system, and to severe allergies and asthma. The investigators noted that these mice had novel Tfh13 cells not found in normal mice. Researchers then took mice with normal immune systems and sensitized them with respiratory and food allergens to induce severe allergic reactions leading to anaphylaxis. While non-allergic mice lacked Tfh13 cells, allergic mice had both Tfh13 cells and a special type of antibody that is linked to allergies and anaphylaxis. These results

[608] www.niaid.nih.gov/news-events/scientists-identify-unique-subtype-eczema-linked-food-allergy
[609] Leung DYM, et al. *Sci Transl Med.* 2019 Feb 20;11(480):eaav2685. PMID: 30787169.
[610] www.niaid.nih.gov/news-events/nih-supported-scientists-demonstrate-how-genetic-variations-cause-eczema
[611] Stevens ML, et al. *Nat*. *Commun.* 2020 Aug 14;11(1):4092. PMID: 32796837.
[612] www.niaid.nih.gov/news-events/scratching-skin-primes-gut-allergic-reactions-food-mouse-study-suggests
[613] Leyva-Castillo JM, et al. *Immunity.* 2019 May 21;50(5):1262-1275.e4. PMID: 31027995.

suggest that Tfh13 cells may be required for allergic disease, including anaphylaxis. Targeting Tfh13 cells may represent a new strategy to prevent or treat allergic diseases.[614,615]

Sesame is among the ten most common childhood food allergies. Only an estimated 20 to 30 percent of children with sesame allergy outgrow it. Severe reactions to sesame are common among sesame-allergic children. Standard allergy tests (the skin-prick test and the allergen-specific antibody test) have been inconsistent in predicting an allergic reaction to sesame. NIAID scientists found that sesame allergy is common among children with other food allergies, occurring in an estimated 17 percent of this population. In addition, the scientists have found that sesame antibody testing, whose utility has been controversial, accurately predicts whether a child with food allergy is allergic to sesame.[616,617] Their findings will need to be validated by additional studies before it can be used in clinical practice.

Improving Treatment and Prevention

The billions of organisms living in and on our body surfaces, collectively called the human microbiome, communicate with each other and the host immune system in a sophisticated signaling network. Interestingly, in limited cases, transferring the microbiome from a healthy person to an unhealthy person can help treat the unhealthy person. Conversely, in other limited cases, transferring the microbiome from an unhealthy person to a healthy person can make the healthy person unhealthy. Researchers are starting to view the microbiome as a new type of treatment. Scientists found that gut microbes from healthy human infant donors transplanted into mice protected animals exposed to milk from experiencing allergic reactions. Conversely, gut microbes transplanted from infants allergic to milk into mice did not protect the mice from developing an allergic rection. These findings suggest that intestinal microbes play a critical role in regulating allergic responses to food and suggest that further research could lead to microbiome-modifying therapies to prevent or treat food allergy.[618] In another example, scientists tested an experimental probiotic treatment for eczema which safely reduced disease severity and increased quality of life for children as young as three years old. The experimental therapy contained strains of live *Roseomonas mucosa*—a bacterium naturally present on the skin. For four months, clinical trial participants or their caregivers periodically applied this probiotic therapy to areas of skin affected by eczema. A majority of the children experienced a greater than 50 percent improvement in eczema severity following treatment on all treated skin sites, including the inner elbows, inner knees, hands, trunk, and neck. In addition, most children needed fewer corticosteroids to manage their eczema, experienced less itching, and reported a better quality of life following the therapy.[619,620]

---

[614] https://www.niaid.nih.gov/news-events/scientists-discover-immune-cell-subtype-mice-drives-allergic-reactions
[615] Gowthaman U, et al. *Science.* 2019 Aug 30;365(6456):eaaw6433. PMID: 31371561.
[616] www.niaid.nih.gov/news-events/nih-researchers-estimate-17-percent-food-allergic-children-have-sesame-allergy
[617] Sokol K, et al. *Pediatr Allergy Immunol.* 2020 Feb;31(2):214-218. PMID: 31657083.
[618] Feehley T, et al. *Nat Med.* 2019 Mar;25(3):448-453. PMID: 30643289.
[619] www.niaid.nih.gov/news-events/probiotic-skin-therapy-improves-eczema-children-nih-study-suggests
[620] Myles IA, et al. *Sci Transl Med.* 2020 Sep 9;12(560):eaaz8631. PMID: 32908007.

Asthma

Asthma is a chronic (long-term) condition that affects the airways in the lungs that may include symptoms such as chest tightness, coughing, shortness of breath, and wheezing. According to the CDC, about 1 in 13 people in the U.S. has asthma.[621] It affects people of all ages and often starts during childhood. For some people, asthma is a minor problem. For others, it can be a major problem that interferes with daily activities and may lead to a life-threatening asthma attack. There is no cure for asthma, but it can be managed through treatment and an asthma action plan. NIH supports research aimed at improving the understanding of asthma, its causes, and how asthma can be prevented and treated in both children and adults.

Understanding Prevalence, Risk Factors, and Underlying Biology

The need for more personalized treatments for asthma is especially important in view of new findings showing that a variety of patient characteristics, such as ethnicity, being overweight/obese, and sensitivity to household allergens, can influence susceptibility to asthma and its severity.[622] Decades ago, NHLBI helped bring inhaled corticosteroids into the clinician's toolbox for asthma, and the Institute now supports research to more precisely tailor interventions based on the variable symptoms, severity, and underlying mechanisms of asthma. The Precision Interventions for Severe and/or Exacerbation-Prone Asthma clinical trial network is beginning to enroll patients with severe asthma at 30 locations nationwide. The trials will evaluate novel and approved treatments for asthma that are specifically targeted to defined groups of patients (e.g., patients who share certain genetic factors or biomarkers).[623,624]

Novel epigenetic markers, which are chemical tags that attach to DNA, may indicate a newborn's risk of developing asthma, according to an international team of scientists led by NIEHS.[625] The data were generated by the Pregnancy and Childhood Epigenetics Consortium and may help researchers identify at birth which children will eventually develop asthma and determine biomarkers of the disease.[626]

The B-WELL-Mom Study, a multicenter prospective cohort study, aims to increase understanding of factors that predict poor asthma control during pregnancy and add to our knowledge of the basic immunology of pregnancy.[627] The maternal immune response to pregnancy suggests that allergy may be an important predictor in determining the clinical course of pregnant women with asthma. NICHD-supported researchers aim to examine in-depth immune function and lung inflammation to assess the impact of immune regulatory processes throughout pregnancy and the postpartum period that may be associated with changes in asthma control. Daily exposure to air pollutants provides another challenge to

[621] https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm
[622] Peters MC, et al. *Am J Respir Crit Care Med*. 2020;202(7):973-982. PMID: 32479111.
[623] https://www.preciseasthma.org/preciseweb/
[624] Wohlford EM, et al. *PLoS One*. 2020;15(5):e0231782. PMID: 32369487.
[625] https://factor.niehs.nih.gov/2019/2/papers/dna/index.htm
[626] Reese SE, et al. *J Allergy Clin Immunol*. 2019; 143(6):2062-2074. PMID: 30579849.
[627] https://www.nichd.nih.gov/about/org/dir/dph/officebranch/bbb/research/B-well-mom

the maternal immune system, both for women with and without asthma. Among persons with asthma, the change in severity/control may be differentially affected by external factors including air pollution.[628]

Hantaviruses are a family of viruses that spread mainly by rodents and can cause varied disease syndromes in people worldwide. NIAID-funded researchers identified a human protein associated with asthma that seems critical to how hantaviruses infect the lungs and sometimes cause hantavirus pulmonary syndrome, a life-threatening pulmonary condition.[629] The most prevalent hantaviruses in North America can recognize the protocadherin-1 (PCDH1) protein) and exploit it to infect the lungs. Using hamsters that lack PCDH1, scientists demonstrated that PCDH1 plays a major role in hantavirus infection of lung cells. However, not all the animals lacking PCDH1 were protected, suggesting that additional routes of infection also exist. The researchers plan to seek out those additional infection pathways as well as investigate therapeutics that might prevent hantaviruses from exploiting PCDH1.

Improving Treatment and Prevention

Asthma guidelines play an important role in guiding health care providers and patients by providing evidence-based recommendations for asthma management. In 2020, NHLBI led an update of the 2007 national asthma guidelines, which help providers and patients make treatment decisions. The updated recommendations include guidance on the use of a new inhaled medication, immunotherapy including allergy shots (injections of an allergen to desensitize the body), and reducing indoor allergens.[630] The guidance is designed to support informed, shared decision-making among primary care providers, specialists, and patients about asthma management.

Recent NHLBI-funded research illustrates the benefits of tailoring asthma interventions based on patient characteristics. One study found that patients with high levels of eosinophils, a cell type that can contribute to airway inflammation, are more likely to respond to inhaled corticosteroid medications than are patients with low eosinophils.[631] Another study examined how African Americans with poorly controlled asthma respond to more intensive treatment options—either a higher corticosteroid dose or the addition of a bronchodilator (a drug to open the airways).[632] While the latter option tends to work best for most African Americans over the age of 12 and for White children, in this study, the two options were about equally likely to work for African American children under the age of 12.

When a child is struggling to breathe or has a painful case of tonsillitis, physicians commonly prescribe drugs called oral corticosteroids, but only for short courses of 14 days or less. Taking corticosteroids for an extended time increases risks for gastrointestinal bleeding, infections, and other health problems. However, the risks associated with short-term use of corticosteroids in children are unclear. NICHD supported scientists who analyzed data on more than one million children who received oral corticosteroids for less than 14 days. Treatment was most often prescribed for children with respiratory infections and allergic conditions. The researchers found that children who took oral corticosteroids for

[628] Pfeffer PE, et al. *Chest* 2021 Apr;159(4):1346-1355. PMID: 33461908.
[629] Jangra RK, et al. *Nature*. 2018; 563(7732):559-563. PMID: 30464266.
[630] https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates
[631] Lazarus SC, et al. *N Engl J Med*. 2019;380(21):2009-2019. PMID: 31112384.
[632] Wechsler ME, et al. *N Engl J Med*. 2019;381(13):1227-1239. PMID: 31553835.

less than 14 days had an increased risk of gastrointestinal bleeding, pneumonia, and sepsis in the month following the start of treatment.[633] The risk of pneumonia and sepsis, which can be fatal, increased twofold. If confirmed in additional studies, these findings call for caution when prescribing oral corticosteroids for children, even for short periods of time.

NIAID awarded funding to establish a clinical research network called Childhood Asthma in Urban Settings.[634] This nationwide network will conduct observational studies and clinical trials to improve our understanding of asthma and develop treatment and prevention approaches tailored to children of low-income families living in urban communities. This new initiative extends and expands NIAID's long-standing efforts to better understand and reduce the disproportionate burden of asthma among children living in low-income urban environments. NIAID intends to provide additional funding over seven years to support this network.

Blood Diseases

NIH supports research on the causes, prevention, and treatment of nonmalignant blood diseases, including anemias, sickle cell disease (SCD), and thalassemia (fewer red blood cells), premalignant processes, such as myelodysplasia and myeloproliferative disorders (dysfunctional growth of bone marrow cells), hemophilia and other abnormalities of hemostasis and thrombosis (dysfunction of bleeding and clotting), and immune dysfunction. Chronic anemias result from a deficiency of red blood cells or an abnormality in hemoglobin production, as is the case with SCD and Cooley's anemia. Patients with chronic anemias can experience pain, fatigue, and other serious health problems. Chronic inherited bleeding disorders, such as hemophilia and von Willebrand disease, leave patients at risk for uncontrollable bleeding. Hundreds of thousands of Americans suffer from one or more types of blood diseases. Every year in the U.S., close to 900,000 emergency department visits are made for anemia.[635] NIH's research on chronic blood disease leads to better understanding, treatment, and prevention of these disorders.

Moving Towards a Cure for SCD by Harnessing the Power of Genetic Therapy

NHLBI launched the Cure Sickle Cell Initiative in 2018 to bring state-of-the-art gene- and cell-based therapies for SCD into first-in-human trials within the next several years. The Initiative considers non-traditional ways to advance research and brings together the SCD community: patients, advocates, caregivers, providers, researchers, industry, and others.[636] Recent progress includes funding of several preclinical studies of emerging therapies. One project focuses on CRISPR gene-editing technology, which can precisely cut out and insert small pieces of DNA to repair a defective gene. The researchers have devised an approach that uses CRISPR to repair the sickle cell mutation in blood-forming stem cells and are performing the studies needed to prepare for an early phase clinical trial in adults with severe SCD.[637]

---

[633] Yao TC et al. *Ann Intern* Med. 2020;173(5):325-330. PMID: 32628532.
[634] https://nihrecord.nih.gov/2021/05/14/nih-establishes-new-network-study-childhood-asthma
[635] https://www.cdc.gov/nchs/fastats/anemia.htm
[636] https://www.nhlbi.nih.gov/science/cure-sickle-cell-initiative
[637] https://www.ucsf.edu/news/2021/12/421901/sickle-cell-clinical-trial-aims-cure-disease-correcting-patients-mutated-gene

If successful, this therapy should be able to permanently cure SCD by fixing the genetic error in the cells that make red blood cells, so that all future red blood cells are disease free.

Developing therapies is hard and unpredictable, so tackling the challenge from multiple approaches using different strategies dramatically increases the chances of success. NHLBI intramural scientists are also working to improve genetic therapy approaches for SCD. They are focusing on higher efficiency methods to insert therapeutic genes into red-blood-cell-producing bone marrow stem cells that could then be delivered to patients. These researchers recently developed an improved virus-based delivery system that is ten times more efficient at incorporating corrective genes into bone marrow stem cells than the most common delivery systems used in this research.[638] The new delivery system will soon be tested in human trials and represents an important step towards a more effective SCD therapy.

Improving Quality of Life for SCD Patients Domestically and in Low- and Middle-Income Countries

Exposure to low levels of chlorine gas, like that found in some household cleaning products, usually only causes mild iteration to the eyes, headache, and dizziness, while exposure to high levels, resembling that in the vicinity of industrial accidents, can cause more severe symptoms, but is rarely life threatening.[639] However, for people with SCD, exposure to the same high concentrations of chlorine gas may lead to acute chest syndrome, a leading cause of death in these patients. NIEHS-funded researchers exposed genetically engineered mice that resembled SCD in humans (sickle mice) and healthy control mice to high levels of chlorine gas or normal air. Hemopexin treatment of sickle mice following exposure significantly improved survival and reduced blood heme levels and lung injury.[640] These results suggest hemopexin treatment may be a new lifesaving therapy for SCD patients exposed to high levels of chlorine gas.

Reducing symptoms and improving the quality of life for those living with SCD is equally important as developing new therapies and cures. Many patients with SCD do not receive interventions proven to reduce pain and the risk of stroke, and some have difficulty or concern regarding side effects.[641] To move proven interventions into broader practice, NHLBI established eight geographically diverse centers that comprise the Sickle Cell Implementation Consortium. One recent consortium study is testing an approach to help patients receive faster treatment for crises by embedding each patient's individualized pain treatment plan in their EHR so that it can be retrieved quickly on a cell phone or tablet during emergency care. In another study, researchers have worked closely with patients to develop a smartphone app to improve adherence to hydroxyurea, a drug proven to reduce crises. The app is now being tested in a clinical trial.[642]

NIH's efforts to relieve suffering for people with SCD extends across the globe to resource-limited countries with less advanced health care systems, such as sub-Saharan Africa, which has the highest SCD burden in the world. The NHLBI-supported Sickle Pan-African Research Consortium is translating successful domestic efforts to African countries by developing a SCD database, establishing standards of

[638] Uchida N, et al. *Nat Commun* 2019 Oct 2;10(1):4479. PMID: 31578323.
[639] https://emergency.cdc.gov/agent/chlorine/basics/facts.asp
[640] Alishlash AS, et al. *Redox Biol* 2021 Aug;44:102009. PMID: 34044323.
[641] Kanter J, et al. *JAMA Netw Open* 2020 May 1;3(5):e206016. PMID: 32469413.
[642] Alberts NM, et al. *JMIR Mhealth Uhealth* 2020 May 8;8(5):e14884. PMID: 32383683.

care, strengthening skills in health and research, and planning research. For example, the consortium has shown that widespread newborn screening for SCD is feasible in sub-Saharan countries, and it has identified opportunities and barriers for achieving sustainability.[643]

Even with effective antiretroviral therapy, people with HIV have a high risk of developing chronic heart, lung, blood, and sleep disorders, compared to people who are HIV-negative. The NHLBI and FIC-supported Heart, Lung, and Blood Co-morbidities Implementation Models in People Living with HIV initiative supports implementation science research to understand and reduce these HIV-related comorbidities,[644] with the goal to achieve earlier detection and prevention. In addition to improving the lives of thousands of people across the world, the strategies and findings are also expected to benefit Americans with HIV living in low-and middle-income regions of the U.S.

Contributing to the high rates of morbidity and mortality in low-resource settings is the lack of low-cost diagnostics that are easy to use and effective at the point-of-care, which often includes rural or remote locations with no access to doctors' offices or diagnostic laboratories, and in some cases no internet or electricity. To help overcome this barrier, NIBIB launched the NIH Technology Accelerator Challenge series of prize competitions to stimulate the design of new diagnostic technologies to transform public and global health and to accelerate the full development of those products for use in low-resource settings.[645] Six winners of the NIH Technology Accelerator Challenge were awarded cash prizes for the design and development of non-invasive, handheld, digital technologies to detect and diagnose SCD, malaria, and anemia.[646,647]

Advancing Other Blood and Blood Disorders Research

NHLBI supports research to protect the Nation's blood supply and to improve the safety and efficacy of blood transfusions through the Recipient Epidemiology and Donor Evaluation Study (REDS). REDS investigators recently found that iron supplements can help correct iron deficiencies in people who donate whole blood frequently,[648] and that a donor's health-related habits (such as smoking or drinking caffeine or alcohol) can impact the quality of stored donated blood and transfusions.[649] Another group of researchers did a genome-wide association study using donated blood samples and identified 27 genetic variables that could influence the shelf-life of stored blood.[650] Further research on these variables could advance donor screening and storage policies and improve transfusion outcomes.

Patients with certain blood diseases, such as leukemia, thalassemia, SCD, and some lymphomas, are treated with a procedure called hematopoietic stem cell transplantation, formerly known as a bone marrow transplantation. It works by first treating the patient with a drug to kill the diseased cells, and

---

[643] Bukini D, et al. *Int J Neonatal Screen* 2021 Feb 26;7(1):12. PMID: 33652550.
[644] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-20-026.html
[645] https://www.nibib.nih.gov/research-program/NIH-Technology-Accelerator-Challenge
[646] https://www.nibib.nih.gov/news-events/newsroom/nih-announces-1-million-prize-competition-target-global-disease-diagnostics
[647] https://www.nibib.nih.gov/ntac-challenge-winners
[648] Mast AE, et al. *Am J Hematol* 2020 Jul;95(7):784-791. PMID: 32243609.
[649] Stefanoni D, et al. *Transfusion* 2020 Jun;60(6):1160-1174. PMID: 32385854.
[650] Page GP, et al. *J Clin Invest* 2021 Jul 1;131(13):e146077. PMID: 34014839.

then intravenously infusing healthy hematopoietic stem cells (HSCs, precursors to all types of blood cells) into the patient to reestablish healthy blood cell production. NIDDK-supported research has identified key approaches for expanding the number of HSCs available for this life-saving procedure by growing them in a laboratory. One approach was the inclusion of a synthetically produced version of the DEK protein that regulates blood cell development. The researchers found that DEK significantly enhanced expansion of cultured mouse and human HSCs within four days.[651] Successfully growing healthy HSCs in culture requires the optimization of dozens of compounds to mimic as closely as possible the natural environment of the body. Another group of NIDDK-supported researchers made four modifications to the culture environment that led to long-term expansion of mouse HSCs. First, they substituted the serum albumin protein with a synthetic compound (polyvinyl alcohol), then they optimized levels of two other components (thrombopoietin and stem-cell factor), and finally they coated the bottom of the culture dish where the cells attach with the fibronectin protein.[652] The next step is to test this new culture system using human HSCs.

Hemophilia is a rare genetic disorder that can cause severe bleeding from a minor cut due to a deficient blood-clotting protein. People with hemophilia A are deficient for the blood-clotting Factor VIII protein, while those with hemophilia B are deficient for Factor IX. NHLBI-funded research helped lead to the development of factor replacement therapy (the infusion of these proteins into the blood) which can prevent dangerous bleeding. However, approximately 30 percent of individuals with hemophilia A develop antibodies against the infused Factor VIII. These antibodies bind Factor VIII and prevent it from working, rendering the therapy ineffective. NHLBI-funded investigators are determining how antibodies against Factor VIII antibodies arise in order to guide development of new therapies that avoid triggering their production. Researchers are also working to develop gene therapy approaches with the potential to avoid the antibody response to Factor VIII, which they plan to test in a phase 1 clinical trial.[653]

Cardiovascular Diseases

Cardiovascular disease (CVD) is a broad term used to encompass many conditions, including heart diseases (e.g., coronary heart disease, cardiomyopathy, heart failure, heart valve disease, sudden cardiac arrest, congenital heart defects), cerebrovascular disease (including stroke), and other disorders and conditions of the blood vessels (e.g., peripheral arterial disease, deep vein thrombosis). Heart disease is the single largest cause of death among men and women in the U.S. Around one-quarter of deaths annually (about 659,000 per year) are caused by heart disease, and about half of Americans have at least one risk factor for heart diseases, such as diabetes, being overweight, poor diet, physical inactivity, high blood pressure, smoking, or excessive alcohol use.[654]

Enhancing CVD Diagnostic Capabilities

Acute coronary syndrome (ACS) is used to describe a range of conditions associated with sudden, reduced blood flow to the heart, such as clot formation in the heart's arteries that block blood flow. ACS is treatable

[651] Capitano ML, et al. *J Clin Invest* 2019 May 20;129(6):2555-2570. PMID: 31107242.
[652] Wilkinson A, et al. *Nature* 2019 Jul;571(7763):117-121. PMID: 31142833.
[653] https://reporter.nih.gov/project-details/9738975#details
[654] https://www.cdc.gov/heartdisease/facts.htm

if diagnosed quickly, but surprisingly, the diverse range of symptoms often makes it difficult for doctors to diagnose. Further, men and women can present with different symptoms, adding another layer of complexity. To help increase the speed and accuracy of ACS diagnosis, NINR-supported researchers evaluated a group of emergency department patients with suspected ACS to better understand the range and severity of their symptoms. They found that symptom severity was more likely associated with ACS in both men and women. Radiation of pain to the jaw, neck, and throat was more likely to be reported by women with ACS, and they were also more likely to experience chest pressure.[655] This study is an important contribution to the understanding of the complexity of the clinical presentation of ACS and the differences between men and women's symptoms.

Atherosclerotic plaque is the build-up of fats and cholesterols in and on the artery walls. It is an important risk factor for CVD, including heart attack and stroke, because if the plaque build-up gets too large it can obstruct blood flow, and if it ruptures it can block smaller arteries in distant locations within the body. Atherosclerotic plaque build-up is normally assessed using a CT scan of the heart. CT scans are also used to help diagnose many other diseases and conditions. If atherosclerotic plaque burden could be assessed routinely on abdominal CT scans, it would enable cardiovascular risk assessment without the need for any additional scanning or radiation exposure, and it may even identify at-risk people much earlier than they would normally be identified. NIH CC researchers showed that using AI can accurately measure the atherosclerotic plaque burden on abdominal CT scans to the same degree as observations by a physician.[656] The automated measurements can also be made more rapidly and without the need for time-consuming and costly manual measurements. With the knowledge gained from this technique, individual patients could receive drug treatment or lifestyle recommendations that could reduce their risk of heart attack and stroke and increase their lifespan.

Many Americans have a cardiac arrhythmia (an abnormal heart rate); the most common type, atrial fibrillation (AFib), affects between three and seven million adults and is a risk factor for strokes. Better detection and monitoring of at-risk individuals would give patients and doctors advanced warning before an adverse outcome, such as a first-time or recurrent stroke, occurred, and could potentially save thousands of lives. One NHLBI-funded team is conducting a clinical trial with patients, their caregivers, health care providers, and computer programmers to develop, validate, and test a new smartphone application that can monitor and detect AFib in people who are at risk for a first-time or recurrent stroke.[657]

Over 97 percent of the human genome sequence does not code for proteins but contains myriads of various gene regulatory elements that help determine when, where, how, how long, and how much of a protein(s) is expressed. They are just as important as the protein coding sequencing in ensuring our bodies function throughout life. They are also less well understood and more difficult to identify and interpret with currently available approaches. NLM researchers are developing advanced computational methods to target and decipher these regulatory elements in cardiac genes, as well as assessing their evolutionary

[655] Mirzaei S, et al. *J Emerg Nurs* 2019 Jul;45(4):357-365. PMID: 30738603.
[656] Summers RM, et al. *Acad Radiol*. 2021 Nov;28(11):1491-1499. PMID: 32958429.
[657] https://www.clinicaltrials.gov/ct2/show/NCT03761394

history and population variation. Their goal is to decipher the component of cardiovascular disorders and disease susceptibility that is not associated with mutations in protein coding genes (3 percent) but is associated with mutations in elements regulating the expression of these genes (the other 97 percent). Computational characterization of gene regulatory elements may aid in determining sequence variation within human populations with respect to disease-susceptibility.[658,659,660,661] This research could help doctors better understand why certain populations are more or less susceptible to CVDs with the hope of improving CVD screenings in at-risk populations. These new methods will be translatable to many other cell types and diseases, dramatically increasing their potential benefit.

Developing New Treatments and Improving Outcomes of Current Treatments for CVD

Congenital heart defects occur in approximately 40,000 individuals in the U.S. each year and are a major cause of infant death.[662] Since it began in 2001, the Pediatric Heart Network (PHN) has been working to improve evidence-based treatment for congenital heart disease.[663] The PHN includes more than 30 children's hospitals with specialized heart disease teams that collaborate to support both state-of-the art care and research. Through a collaborative review of surgeries for two common heart defects, tetralogy of Fallot (TOF) (combination of four heart defects causing the heart to pump out oxygen-poor blood) and narrowing of the aorta, network researchers developed new postsurgical guidelines that cut the amount of time that the infants spent on a breathing tube by 80 percent. These new guidelines also reduced the cost of TOF surgery by 27 percent.[664]

For decades, there has been uncertainty about how to treat the most deadly and common type of heart disease, ischemic (or coronary) heart disease, in which the arteries become blocked and cannot pump enough blood to the heart. To address this challenge, NHLBI-supported the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches clinical trial to compare two common approaches for managing ischemic heart disease. In this study of more than 5,000 patients, half were treated with an invasive approach that included stenting, bypass surgery, and medications, while the other half were treated with lifestyle changes and medications but not surgery. The study found that both approaches produced similar outcomes after three years of follow-up. However, the invasive approach offered better symptom relief and quality of life for patients with chest pain.[665,666] These results will help inform better decisions about the best treatment options for patients.

For nearly 16 years, the NHLBI-supported Cardiothoracic Surgical Trials Network (CTSN), which brings together scientists and surgeons at medical sites across the country to move research from the proof-of-concept stage into clinical trials, has played a key role in designing and conducting collaborative clinical

---

[658] Li S, et al. Genome Biol. 2019 Jul 15;20(1):140. PMID: 31307522.
[659] Zhu I, et al. *Nucleic Acids Res* 2021 May 7;49(8):4493-4505. PMID: 33872375.
[660] Kvon EZ, et al. *Cell* 2020 Mar 19;180(6):1262-1271.e15. PMID: 32169219.
[661] Li S and Ovcharenko I. *Genomics* 2020 May;112(3):2261-2270. PMID: 31887344.
[662] https://www.cdc.gov/ncbddd/heartdefects/data.html
[663] https://www.nhlbi.nih.gov/science/pediatric-heart-network-phn
[664] McHugh KE, et al. *Ann Thorac Surg* 2019 May;107(5):1421-1426. PMID: 30458158.
[665] Maron DJ, et al. *N Engl J Med* 2020 Apr 9;382(15):1395-1407. PMID: 32227755.
[666] Spertus JA, et al. *N Engl J Med* 2020 Apr 9;382(15):1408-1419. PMID: 32227753.

trials aimed at improving surgical treatments for CVD.[667] In 2019, NHLBI renewed the CTSN, which launched a new phase 3 clinical trial to examine how to manage patients after coronary artery bypass surgery, in which blood vessels from elsewhere in the body are rerouted or transplanted to substitute for blocked coronary arteries. After this surgery, many patients develop AFib, which is treated with antiplatelet therapies such as aspirin. The trial is evaluating whether adding oral anticoagulants (blood thinners) to antiplatelet therapy can increase the long-term outcomes by further reducing the risk of heart attack and stroke for such patients.[668]

Approximately 6.2 million adults in the U.S. are living with heart failure, in which the heart fails to pump enough blood to meet the body's needs, and in 2018 roughly 13 percent of all death certificates mentioned heart failure.[669] Fifty percent of all heart failure is associated with preserved ejection fraction (HFpEF), where the heart contracts normally, but fills with blood too slowly. HFpEF has limited treatment options. To help spur new research into this condition, NHLBI developed HeartShare, a new funding opportunity to conduct large-scale analysis of clinical, laboratory, and imaging data from patients with HFpEF to characterize mechanisms of the disease and identify therapeutic targets.[670]

Individuals with lupus, an autoimmune disease where the body's immune system attacks its own tissues and organs, are at increased risk of developing premature CVD. Prior research conducted by NIAMS researchers demonstrated that the drug tofacitinib improves clinical features of CVD in a mouse model of lupus. A recent NIAMS-supported Phase 1b/2a randomized, double-blind, placebo-controlled clinical trial in lupus patients indicated that tofacitinib treatment was safe and showed promising secondary outcomes. The patients had improved cardiometabolic and immunological indicators associated with reduced atherosclerosis, or plaque buildup in arteries. Interestingly, lupus patients who carry a genetic risk factor, called the *STAT4* risk allele, have more severe lupus disease and are at significantly increased risk for CVD. While examining data from the trial, researchers found that individuals in the study who had the *STAT4* risk allele had a more robust response to tofacitinib, a finding that has implications for precision medicine approaches to prescribing the drug if confirmed in a larger trial.[671]

Heart disease is the most common cause of death among older Americans. Cholesterol-lowering drugs known as statins are used to prevent heart attacks, strokes, and other life-threatening events associated with heart disease; however, no previous large studies have evaluated the safety of using statins after the age of 75. Recently, NIA-supported researchers analyzed medical records of more than 327,000 military veterans and found that adults 75 and older who start statins for the first time may have a lower risk of death than those that do not start statins.[672] This retrospective evidence, while compelling, is not definitive. NIA is currently supporting a clinical trial, Pragmatic Evaluation of Events and Benefits of Lipid-

[667] http://www.ctsurgerynet.org/
[668] https://clinicaltrials.gov/ct2/show/NCT04045665
[669] https://www.cdc.gov/heartdisease/heart_failure.htm
[670] https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-21-015.html
[671] Hasni SA, et al. *Nat Commun* 2021 Jun 7;12(1):3391. PMID: 34099646.
[672] https://www.nia.nih.gov/news/using-statins-first-time-may-reduce-risk-death-among-adults-75-and-older

Lowering in Older Adults,[673,674] that will enroll 20,000 people to examine the overall benefits and risks of statins in adults 75 and older without heart disease, and is expected to be completed in 2026.

When the fine-tuned molecular mechanisms of blood vessel development go awry, vascular abnormalities such as hemangiomas of infancy occur. Hemangioma is a common vascular birthmark made of extra blood vessels in the skin. Most hemangiomas, found in up to ten percent of newborns and at an even higher incidence in premature infants, do not require treatment. However, a significant number of them cause substantial disease through compression of vital structures, pain from ulceration, and scarring, and thus require systemic therapies. Propranolol, used widely in adults to treat high blood pressure, chest pain, and uneven heartbeat, is a common treatment, but has unwanted side effects. NIAMS-supported researchers studying this condition in mice found a way to leverage the beneficial parts of propranolol treatment without the negative side effects.[675] These findings could lead to new treatments for hemangiomas of infancy and other blood vessel diseases affecting patients of all ages.

Improving Quality of Life for CVD Patients

Heart failure occurs when the heart muscle does not pump blood as well as it should, leading to fluid to build up in the lungs and legs, which causes shortness of breath and swelling of the legs and feet. NINR-supported scientists used a web-based mobile health application to measure symptoms of heart failure in a racially and ethnically diverse patient population to better understand their experiences and identify potential solutions to help alleviate the symptoms. They found that better health status was associated with higher physical function and the ability to participate in social roles and activities, while lower health status was associated with dyspnea (shortness of breath).[676] These findings suggest that the health status of individuals living with heart failure can be improved by modifying behaviors and reducing risk factors, such as taking steps to decrease dyspnea, engaging in more physical activity, and becoming more involved in social situations and taking on more social roles.

One of every three Americans will die of heart disease, making it not only one of the most common causes of death, but also a common cause for post-treatment rehabilitation. NIA-supported investigators found that an innovative cardiac rehabilitation intervention improved physical function, frailty, quality of life, and depression in hospitalized heart failure patients, as compared to traditional rehabilitation programs. The team developed customized exercise programs that emphasized improving balance, strength, mobility, and endurance, and began the intervention during a patient's hospital stay whenever feasible instead of waiting until the traditional six weeks after discharge. Compared to a control group that received usual cardiac rehab care, participants showed marked gains in measures of physical functioning and overall quality of life, as well as notable improvements in self-perception of their health status and depression surveys compared to pre-trial baselines.[677,678] These results demonstrate that

[673] https://clinicaltrials.gov/ct2/show/NCT04262206
[674] https://www.nia.nih.gov/news/could-taking-statins-prevent-dementia-disability
[675] Sasaki M, et al. *NPJ Precis Oncol* 2019 Nov 1;3:27. PMID: 31701018.
[676] Baik D, et al. *Eur J Cardiovasc Nurs*. 2019 Apr; 18(4): 325–331. PMID: 30681003.
[677] https://www.nia.nih.gov/news/tailored-earlier-cardiac-rehab-program-shows-physical-emotional-benefits-heart-failure
[678] https://clinicaltrials.gov/ct2/show/NCT02196038

tailored interventions that target heart failure's related decline in physical abilities can result in real overall benefits for patients.

Obesity-related diseases, including high blood pressure and other heart conditions, increase a person's risk of having a stroke. A stroke happens where there is a loss of blood flow to part of the brain. Restoring brain function after a stroke can be challenging. Functional recovery from brain damage requires networks of nerves to adapt and reorganize. This "neuroplasticity" naturally occurs during early development, but studies in rodents suggest that there is a brief period of similarly high neuroplasticity after a stroke.[679] Intensive motor training provided to rodents during this window can lead to nearly full recovery, but no evidence for a similar recovery window in humans has been found. A recent study, supported by NINDS, NICHD, and NIDCD, found that intensive therapy, added to standard rehabilitation, produces the greatest improvement when administered two to three months after a stroke. These results could lead to improved rehabilitation programs for stroke patients.[680] The results suggest that there is a critical time window for rehabilitation following a stroke. Larger clinical trials are needed to better delineate the timing and duration of this critical window and to determine what dose of therapy would achieve the best results.

Researching CVDs in Different Patient Populations

NHLBI continues to advance research to improve the health of American Indian communities. In 2019, NHLBI renewed its long-standing commitment to the Strong Heart Study,[681], established in 1988, and is the largest epidemiological study of CVD and its risk factors in American Indians. The study involves a partnership with 12 Tribal Nations, and has followed more than 8,000 participants, many of whom live in low-income, rural areas of Arizona, Oklahoma, and the Dakotas. Recent research topics included tribal perspectives on privacy and data sharing, environmental exposures to heavy metals, such as arsenic, and CVD risk, the role of DNA methylation (adding a small molecule to DNA that changes the activity without changing the sequence) on CVD risk and development, and the effects of unhealthy habits, including smoking and binge drinking, on CVD risk and development.[682] This new study includes more funding for community-driven pilot projects, and continued emphasis on training and development.

A study by NIEHS-funded researchers provides insight into how SARS-CoV-2 damages heart cells. Researchers exposed three types of human heart cells, cardiomyocytes, cardiac fibroblasts, and endothelial cells, to small amounts of the SARS-CoV-2 virus. The virus was only able to infect and replicate in cardiomyocytes, the heart muscle cells, which were the only ones that have Angiotensin-Converting Enzyme 2 (ACE2) receptors on their surface. These receptors serve as the cellular entry point for the virus. Infected cardiomyocytes showed structural defects and had decreased expression of genes important in heart contraction. Many cardiomyocytes were missing nuclear DNA, without which cells cannot

[679] Biernaskie J, et al. *J Neurosci*. 2004 Feb 4;24(5):1245-54. PMID: 14762143.
[680] Dromerick AW, et al. *Proc Natl Acad Sci U S A*. 2021 Sep 28;118(39):e2026676118. PMID: 34544853.
[681] https://strongheartstudy.org/
[682] https://strongheartstudy.org/Research/Papers-and-Abstracts/Published-Papers

function.[683,684] These findings may inform treatment strategies to protect heart health in COVID-19 patients.

Over the past 30 years, scientists and clinicians across the world have successfully transformed HIV/AIDS from a deadly disease with no treatment into a chronic disease that can be managed with little to no symptoms. A major reason for this is the advent of combination antiretroviral therapy (cART), which is a treatment that uses a combination of three or more drugs to treat HIV infection. Although cART treatment has saved millions of lives, some of the earlier antiretroviral drugs were associated with increased risks for CVD. NIEHS-researchers are studying the potential cardiac toxicity of a specific cART regimen following early life exposure to this lifesaving drug.[685] This research should help doctors better monitor HIV-infected patients who were prescribed these older drugs early in their life.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a serious, long-term illness that affects many body systems and is characterized by fatigue caused by mental or physical activity. There are no established tests to diagnose ME/CFS, and no known treatments or cures. Causes of ME/CFS may vary and many cases have no known cause. An estimated 836,000 to 2.5 million Americans have ME/CFS, though most of them have not been diagnosed.[686] NIH seeks to discover the basic mechanisms associated with ME/CFS, identify treatments, and support research that will improve the lives of people with ME/CFS.

An NINDS Advisory Council Working Group for ME/CFS Research released a report in 2019 detailing strategies to address gaps and opportunities in ME/CFS research.[687] The report identified critical gaps including the lack of knowledge of the underlying biological mechanisms of ME/CFS and insufficient information about clinical aspects of the disease, a low number of investigators and NIH grant applications focusing on ME/CFS, particularly from early-career investigators, and the lack of an overall research plan. This report serves as a road map for advancing ME/CFS research to more effectively and quickly find treatments and therapies that improve the lives of people living with ME/CFS.

NINDS-funded researchers examined biochemical reactions involved in energy production, or metabolism, in two specific types of immune cells obtained from healthy people and people with ME/CFS.[688] The team used state-of-the-art methods to look at energy production by the mitochondria when the cells were in a resting state and after they had been activated. Mitochondria are biological powerhouses and create most of the energy that drives cells. The findings revealed disruptions in the way immune cells produce energy, providing additional evidence for the role of the immune system in ME/CFS,

---

683 https://factor.niehs.nih.gov/2021/7/papers/dert/index.htm#a2
684 Perez-Bermejo JA, et al. *Sci Transl Med* 2021 Apr 21;13(590):eabf7872. PMID: 33723017.
685 https://reporter.nih.gov/search/4AbJHpQj80Wunj2Tjipq4Q/project-details/10505813#publications
686 National Academies of Sciences, Engineering, and Medicine. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. 2015. https://doi.org/10.17226/19012
687 Report of the NANDS Council Working Group for ME/CFS Research. 2019. www.ninds.nih.gov/sites/default/files/migrate-documents/report_of_nands_council_working_group_for_mecfs_research_508c_0.pdf
688 https://www.ninds.nih.gov/News-Events/News-and-Press-Releases/Press-Releases/energy-use-by-me-cfs-immune-cells-study

including providing important clues to better understand the mechanisms underlying this devastating disease.

New research funded by NCCIH sheds light on post-exertional malaise (PEM) in ME/CFS. PEM is the worsening of symptoms following even minor physical or mental exertion and can affect every part of the body, often interfering with an individual's ability to lead a normal life.[689] While symptoms vary, researchers identified three core symptoms that can assist in better diagnosing patients: exhaustion, cognitive difficulties, and neuromuscular complaints. Patients describe PEM as all-encompassing disease which is difficult to predict or manage and that requires complete bedrest for full or partially recovery. Further research identifying subtypes of PEM could lead to better targeted therapeutic options and better understanding of patients' mental health and recovery requirements.

Chronic Pain and Palliative Care

Acute pain is triggered in the nervous system as a response to possible injury and directs individuals to attend to, avoid, or resolve stimuli that may be of immediate danger. It is a protective mechanism that works to prevent lasting damage to the body. In contrast, chronic pain is a debilitative phenomenon that alters the function and response of pain sensors in the body and the brain. Chronic pain can persist for weeks, months, years, or even a lifetime. 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, negatively affecting an individual's quality of life. Results from the 2019 National Health Interview Survey show that 20.4 percent of adults had chronic pain and 7.4 percent of adults had chronic pain that frequently limited life or work activities (referred to as high impact chronic pain) in the past three months.[690]

Studies of Chronic Pain

Ongoing research to better understand chronic pain provides insight on chemical and biological mechanisms that contribute to the perseverance of pain in afflicted individuals. Discoveries in this field are further facilitated by research partnerships and programs.

The Pain Management Collaboratory (PMC), established in 2018 via a partnership between the NIH, DoD, and VA, tests the implementation and evaluation of nonpharmacologic approaches for the management of pain and common co-occurring conditions in the military and veteran health care systems. The PMC funded 11 large-scale, multisite, clinical trials and a resource coordinating center called the Pain Management Collaboratory Coordinating Center.[691] These trials focus on real world effectiveness of interventions for the management of pain and includes complementary health interventions such as spinal manipulation, screening/brief intervention/referral to treatment, physical therapy, and mindfulness. It also includes a percutaneous (needle-puncture of the skin) peripheral nerve stimulation device for postsurgical pain, a noncomplementary health intervention. Each current study includes some

[689] Stussman B, et al. *Front Neurol* 2020;18(11):1025. PMID: 33071931.
[690] https://www.cdc.gov/nchs/products/databriefs/db390.htm
[691] https://painmanagementcollaboratory.org/

level of implementation science, with most studies focusing on pre-implementation (e.g., identification of potential barriers to adoption of the intervention).

An associated collaboration, the Collaborative Care for Chronic Pain in Primary Care (PPACT) study, part of the NIH Pragmatic Trials Collaboratory and supported by the NIH Common Fund, found that patients who participated in the PPACT intervention as part of their regular care for chronic pain showed improved function and reduced pain compared to standard treatment. However, patients did not reduce their use of opioid medication.[692] The study was conducted under real-world conditions in Kaiser Permanente primary care clinics across three U.S. regions (Georgia, Hawaii, and Northwest) to determine the effectiveness of a group-based cognitive behavioral therapy intervention for chronic pain and functional impairment in patients receiving long-term opioid therapy.

The NIH Common Fund also supports the Acute to Chronic Pain Signatures program,[693] which recently achieved a major milestone; beginning recruitment for a clinical study to identify and understand biomarkers, or biological signals, that can help predict a person's pain experience following knee or thoracic surgery. The purpose of this program is to develop a set of objective biomarkers that provide signatures that can be used to help predict which patients will recover from acute pain associated with surgery or injury and which ones will develop long-lasting chronic pain. This information will help guide evidence-based approaches to pain management. The program will collect neuroimaging, sensory testing, and psychosocial data for several months after the acute pain event to form a comprehensive data set. Analyzing the data could help researchers develop ways to predict which patients will recover and which patients will develop long-lasting chronic pain.

A new study by NCCIH and JPA Health Communications sheds light on how pain patients and health care providers interact on the social media platform Twitter.[694] The researchers analyzed the Twitter audiences most engaged in pain and oncology topics using social network analysis (SNA). An SNA is the analysis and visualization of large networks of connected users on Twitter, and it provides insight into the social engagement of accounts focused on the specific topics and flow of information between these accounts. Researchers assessed Twitter relationships within the pain and oncology SNAs and compared the strength of the relationships between the patient and health care practitioner audiences within each SNA. They found that on Twitter, pain patients and providers appear to interact less than oncology patients and providers. This finding shows that challenges in communication do not just occur in face-to-face interactions, but also in digital social network interactions. This challenge serves as an additional roadblock to what can be shared decision-making opportunities around pain management. The research also illustrates how such social media networks may be used to better understand the relationships, language gaps, and resources shared by pain patients and their providers. Furthermore, it offers a template for using digital social network interactions to research other difficult-to-treat or rare disease patients. This may be especially relevant because social media platforms are important tools for patient

[692] https://reporter.nih.gov/project-details/9315954
[693] https://commonfund.nih.gov/pain
[694] Kloth YM, et al. *PLoS One.* 2019;14(12):e0226321. PMID: 31877158.

engagement, and research has found that participating in online communities may improve health outcomes for certain conditions.

HEAL Initiative

NIH's principal program to safely address pain is the HEAL Initiative, an aggressive, NIH-wide effort to accelerate finding scientific solutions to stem the national opioid public health crisis.[695] Almost every NIH IC is involved in HEAL to address this public health emergency. Researchers associated with the HEAL Initiative are leveraging a variety of strategies to address the opioid epidemic, including through understanding, managing, and treating pain as well as through improving prevention and treatment for opioid misuse and addiction. The initiative supports a wide range of research to enhance pain management including uncovering the underlying biology of pain and targets to facilitate early-stage development of non-opioid pain treatment, translating discoveries into clinical pain research, and advancing promising pain treatments through clinical research to be tested in humans. Development of non-addictive pain treatments and therapeutics are of significant interest to doctors, patients, pain researchers, and others working to end the national opioid public health crisis. Research in this area ranges from pharmaceutical approaches to mental health treatments and holistic treatments for chronic pain.

Preclinical Studies

The HEAL program, Discovery and Validation of Novel Targets for Safe and Effective Treatment of Pain, seeks to accelerate the scientific discovery and validation of novel treatment targets for acute and chronic pain conditions.[696] The goals of the program are to enable the basic research discovery of biological targets in the peripheral and central nervous system, as well as in the immune and other tissue systems in the body that are critically involved in detecting and transmitting painful signals under pathological and disease conditions, accelerate rigorous validation of targets for the development of effective treatments for pain, with minimal side effects and little to no abuse or addiction liability, and establish multiple pain therapeutic targets for small molecules and biologics, such as antibodies and cell-based therapies that could lead to translational and clinical studies and testing in humans. Through 2021, 34 projects have been funded.

Another HEAL program, Discovery and Validation of Biomarkers, Endpoints, and Signatures for Pain Conditions, supports biomarker discovery and rigorous validation to advance the clinical development of non-addictive pain treatments toward phase 2 clinical trials and beyond.[697] Identifying biomarkers for pain conditions could help accelerate the development of therapeutics for pain by improving patient selection for therapeutic clinical trials. Researchers plan to use biomarkers to assess individuals' pain levels and responses to various treatment regimens and to predict the development of chronic pain after injury. In the long term, this research will provide translational tools that can help prevent chronic pain and reduce

[695] https://heal.nih.gov/
[696] https://heal.nih.gov/research/preclinical-translational/novel-targets
[697] https://heal.nih.gov/research/preclinical-translational/biomarkers

opioid use in patients who do not respond to opioids. Projects prioritize the discovery of biomarkers, biomarker signatures, and endpoints for pain. Through 2021, nine projects have been awarded.

The Translating Discoveries into Effective Devices to Treat Pain supports the development of next-generation medical devices to diagnose and treat pain by supporting preclinical development and demonstration of safe, effective, and non-addictive device-based technologies and approaches.[698] It will also support the translation of promising devices into clinical trials that will inform function, final design, safety, and/or efficacy. Researchers will pursue multiple avenues for treating pain caused by injury or disease, including the use of implanted devices, such as electrodes, and noninvasive targeted stimulation of nerve cells and regions of the brain associated with pain perception, with consideration of individual anatomical differences to increase efficacy. Through 2021, 15 projects have been funded.

The Translational Research to Advance Testing of Novel Drugs and Human Cell-Based Screening Platforms to Treat Pain and Opioid Use Disorder Program is led by NCATS with support from the NIH HEAL Initiative, NHLBI, NIAMS, NIBIB, NICHD, NIDCR, NIDA, and NINDS. This program aims to advance novel drugs and screening platforms to better address and treat both pain and opioid use disorder (OUD) by supporting collaborative research projects, prize awards, research grants, and supplements.[699] Research examples from the program include the following: pre-clinical testing of candidate therapeutics for the treatment of pain and OUD, identification of potential therapies that work in novel ways, development and high-throughput screening methods to test candidate therapeutics, and elucidation of promising chemical structures for therapeutic candidates.

NCATS, with support from the NIH HEAL Initiative, is applying translational science approaches to advance new treatments for opioid addiction and pain. Tissue chip devices, which are 3-D platforms made to support living human tissues and cells, are designed as accurate models of the structure and function of human organs, such as the lungs, liver, and heart. Tissue chips closely mimic human physiology, which make them useful as models for studying biological processes and testing the toxicity, safety, and efficacy of drugs. In the first phase of funding, researchers will develop and validate the nociception, addiction, or overdose characteristics of the tissue chips. In the second phase, researchers will, test the functionality of the tissue chips to understand pain or opioid pathway mechanisms, characterize tissue responses to pain or opioid therapeutics, and identify new treatments for pain or addiction or offer insights into improving current treatment efficacy.[700]

Translational Studies

To evaluate potential novel therapeutic agents, HEAL has established models to rigorously profile, screen, and validate assets in an optimized Preclinical Screening Platform for Pain (PSPP). PSPP uses a tiered approach to evaluate in vitro and in vivo abuse liability, pharmacokinetics, and side effect profiles of promising small molecules, biologics, natural products, and devices, and evaluates the asset in models relevant to human pain conditions.[701] NIH staff assess the suitability of assets for acceptance into the PSPP

[698] https://heal.nih.gov/research/preclinical-translational/discoveries-into-devices
[699] https://heal.nih.gov/research/preclinical-translational/novel-drugs-screening-platforms
[700] https://ncats.nih.gov/tissuechip/projects/pain-addiction-overdose
[701] https://heal.nih.gov/research/preclinical-translational/screening-platform

and direct the preclinical testing of submitted assets, which contract facilities perform in a blinded manner at no cost to PSPP participants. The evaluation of a submitted compound for suitability for testing in the PSPP begins with an assessment of the proposed scientific rationale. Accepted agents are evaluated, and the PSPP provides participants with feedback on results and recommends next steps in the process. The PSPP is continuously accepting compounds for evaluation. Researchers from academia and industry in the U.S. or abroad are eligible to submit compounds for screening. Through 2021, the contract supports testing of approximately 30 assets.

Clinical Studies

HEAL's Back Pain Consortium is a new patient-centered translational research initiative that will use an integrated model to examine how interactions among components of the body contribute to chronic low back pain.[702] It also will examine readily available therapeutic strategies that involve multiple interventions, either together or in sequence, that treat the mind and the body, and will promote the development of new technologies for back pain diagnosis and treatment. This highly collaborative research program aims to deliver an integrated model of chronic low back pain, as well as tailored treatment approaches for individuals with musculoskeletal pain.

The NIDDK-led Hemodialysis Opioid Prescription Effort (HOPE) consortium is developing interventions that may reduce opioid prescriptions for people receiving hemodialysis while maintaining pain control and enhancing quality of life.[703] The program will initiate multipronged (behavioral, cognitive, and medical) pain treatments tailored individually to each patient and use novel strategies to reduce dependence on opioids in affected patients. The consortium will evaluate chronic opioid prescription rate, prescription drug dose, pain control, patient satisfaction with care, perception of quality of life, hospitalization rates, and mortality. HOPE researchers will also examine comorbid illnesses and social determinants of health to identify novel risk factors for pain and opioid use in this population.

The Pain Management Effectiveness Research Network is a multisite research cooperative program that aims to improve pain care by evaluating the effectiveness of a broad range of therapies to guide clinical practice in real-world settings.[704] The program supports clinical trials that compare the effectiveness of existing non-addictive therapies or of existing or novel approaches for prevention and management of pain. Ultimately, the results will identify the most effective interventions and management strategies for pain while reducing reliance on opioids, improve functional outcomes, and reduce pain. Grants were awarded to fund clinical trials at six institutions and supplements awards were provided to six institutions to support clinical trial infrastructure.

The Early Phase Pain Investigation Clinical Network (EPPIC-Net)[705] aims to enhance the treatment of high-impact pain conditions and reduce reliance on opioids through early-phase clinical trials of nonaddictive pain treatments at 12 specialized clinical centers. EPPIC-Net launched its first clinical trial of a novel asset for the treatment of knee osteoarthritis. The network has the capacity to conduct many simultaneous,

[702] https://heal.nih.gov/research/clinical-research/back-pain
[703] https://clinicaltrials.gov/ct2/show/NCT04571619
[704] https://heal.nih.gov/research/clinical-research/pain-management-research
[705] https://heal.nih.gov/research/clinical-research/eppic-net

multisite studies on a variety of treatments, including drugs and devices, as well as studies to better understand pain. Examples of funded projects include those that will test new pain treatments (e.g., small molecules, biologics, devices) with go/no-go criteria in early-stage trials to move toward efficacy trials for regulatory approval. Other examples include those that will provide proof-of-concept clinical testing of potential biomarkers and new treatments to help identify specific pathways or mechanisms that hold promise for future therapeutic development. Through 2021, 14 grants and three clinical trials have been funded.

Recent decades have seen an overreliance on the prescription of opioids for chronic pain, which has contributed to an epidemic of opioid overdose deaths and addiction. The Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) initiative supports multiple pragmatic trials to conduct research embedded in health care systems.706 These trials aim to determine the effectiveness of multiple non-opioid interventions for treating pain and assess the impact of implementing interventions or guidelines to improve pain management and reduce reliance on opioids. By the end of FY 2020, through the NIH HEAL Initiative and support from several ICs, approximately $32 million was awarded to seven PRISM projects. Each awardee was required to conduct a pragmatic clinical trial aimed at improving the availability and effectiveness of evidence-based, non-drug pain management. The projects funded in 2019 and 2020 focused on testing the use of decision support tools embedded in EHRs, improving patients' role in managing their chronic pain, and evaluating the effectiveness of incorporating a billable mindfulness-based stress-reduction program into a primary care treatment for chronic low back pain.

In response to an urgent need for effective strategies to meet the needs of people with OUD who also live with chronic pain, the NIH HEAL Initiative and NIDA established the Integrative Management of Chronic Pain and OUD for Whole Recovery (IMPOWR) research program.[707] IMPOWR is focused on establishing integrated patient-centered treatment interventions and models of care delivery that reach underserved communities such as African Americans, AI/AN, Hispanic/Latino, and rural populations. By the end of 2021, a total of $19.7 million was awarded to support four research centers and one resource coordinating center in the development and testing of combined interventions that include psychotherapy, medications for OUD, exercise, and pain self-management in specific healthcare system settings. Research in the IMPOWR network will focus on the whole patient, recognizing the influence of stigma, health inequities, and co-occurring psychiatric disorders.

The NIH HEAL Initiative also seeks to expand diversity in chronic pain research by providing funding through supplement awards to address challenges related to meaningful engagement of populations experiencing pain and OUD in HEAL clinical studies.[708] These efforts are developed in the context of individual studies, settings, and patient populations to enhance engagement of patients, communities,

[706] https://heal.nih.gov/research/clinical-research/prism
[707] https://heal.nih.gov/research/clinical-research/integrative-management-chronic-pain
[708] https://heal.nih.gov/research/cross-cutting-research/participant-diversity-inclusion-engagement

and other stakeholders, and to improve recruitment, retention, and inclusion of participants from racial and ethnic minority populations.

NIBIB-supported researchers are adopting a minimally invasive, safer approach to electrically treating pain directly at the source as part of the HEAL Initiative.[709] Neuromodulation therapies apply electrical stimulation to nerves to treat conditions including chronic lower back pain, paralysis, incontinence, migraines, sleep apnea, and obesity. Currently, the most effective neuromodulation treatments require intricate surgical procedures to implant a complex device that is invasive and expensive, making it a last resort treatment. The key innovation is a new type of electrode that may make neuromodulation therapies less invasive, less costly, less painful, more reliable, and much easier to scale for a larger number of patients.

Impact of Disease on Chronic Pain

As scientists learn more about the causes of chronic pain, it is becoming clear that disease state and biology play a major role in how patients experience pain. Studies in this area provide insights into how therapeutics and treatments might be developed for people experiencing chronic pain as a symptom of disease or illness.

The NIDDK-led Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network conducts innovative, collaborative studies of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome that include searching "beyond the bladder/prostate" to find the causes of these conditions. It includes studies of the possible relationships between these conditions and other chronic pain disorders, such as irritable bowel syndrome and fibromyalgia.[710] Beginning in FY 2019, a three-year MAPP Research Network Extension Phase has enabled characterization of participants currently enrolled in network studies for an additional 12 months, enriching the network's unique clinical dataset and biological sample archive and allowing for unprecedented assessment of disease progression over time.

Fibromyalgia is a disorder that involves widespread pain, tenderness, and fatigue, among other symptoms. Results of a recent NCCIH study found pain at the time of testing, rather than the presence of a chronic pain condition, is primarily responsible for changes in the functioning of the brain's default mode network in patients with fibromyalgia.[711] The default mode network, which includes different brain regions that are highly connected to each other at specific times, is active when a person is at rest (awake but not engaged in an attention-demanding or goal-oriented task). It becomes inactive when the person starts to perform a task. These results suggest that transient changes due to the current experience of pain may be a substantial contributor to default mode network connectivity disruptions in chronic pain patients. NCCIH researchers reported that even though immediate pain and the long-term experience of having a pain condition probably influence each other, the specific effects of each of them need to be considered when studying functional brain connectivity in chronic pain patients.

---

[709] https://www.nibib.nih.gov/research-program/medical-devices-to-treat-pain
[710] http://www.mappnetwork.org/
[711] Ceko M, et al. *Neuroimage* 2020; 1;216:116877. PMID: 32344063.

Sex also plays a role in how patients experience chronic pain. NIAMS-supported researchers demonstrated that the miR-19b microRNA in the blood serum is influenced by estrogen, a hormone present in higher levels in females, and exposure to traumas, such as a motor vehicle collision or sexual assault.[712] The observed expression levels of this microRNA indicate a sex-dependent difference in vulnerability to posttraumatic widespread pain and posttraumatic stress symptoms. Furthermore, miR-19b regulation appears to affect the circadian rhythm (the body's 24-hour sleep/wake cycle) and implicates circadian rhythm genes in the development of posttraumatic pain and stress symptoms.

Palliative Care

Palliative care is specialized medical care for people living with a serious, often terminal, illness, focusing on providing relief from the symptoms, such as pain, nausea, constipation, and trouble sleeping.[713] Palliative care can be received at the same time as treatment for a disease or condition with the goal of preventing or easing suffering, improving quality of life for both the patient and their family, and helping patients and their families make difficult health care decisions.

Approximately 90 million people in the U.S. are living with serious illness and would benefit from end-of-life and palliative care. However, there remains a gap in broader access to and receipt of this care for some individuals, such as those who do not require hospitalization and are not eligible for hospice services. NINR aims to stimulate research focused on determining the needs and best practices for the integration of palliative care into home and community settings.[714] Home- and community-based palliative care programs ensure that those with serious, advanced illness who do not require hospitalization, but are not appropriate for hospice, have access to high quality end-of-life and palliative care.

Craniofacial, Dental, and Oral Diseases

Dental, oral, and craniofacial diseases have affected almost all Americans at some point in their lives. From cavities to periodontal (gum) diseases, chronic dental diseases can affect health and well-being. CDC estimates that 90 percent of Americans between the ages of 20 and 64 have had cavities in their permanent teeth[715] and 42 percent of adults aged 30 years and older have some form of periodontal disease.[716] Tooth decay is the most common chronic disease among young teens ages 12 to 15 years and is six times more common than asthma among 12- to 14-year-olds. NIH supports a research portfolio dedicated to understanding and treating dental, oral, and craniofacial diseases. NIDCR is the federal government's lead agency for scientific research in this area. Other NIH ICs, including NIAMS and NICHD, also contribute to NIH's portfolio in this area.

Four out of every ten U.S. adults has some form of periodontal disease.[717] Periodontal disease is an infection of the soft tissue surrounding the teeth, and without treatment, can destroy the bone that

[712] Linnstaedt SD, et al. *Pain* 2020 161(1):47-60. PMID: 31569141.
[713] Teoli D, Kalish VB. *Palliative Care*. StatPearls 2022. https://www.ncbi.nlm.nih.gov/books/NBK537113/
[714] https://grants.nih.gov/grants/guide/pa-files/PAR-19-321.html
[715] https://www.nidcr.nih.gov/research/data-statistics/dental-caries/adults
[716] https://www.nidcr.nih.gov/research/data-statistics/periodontal-disease/adults
[717] https://www.cdc.gov/oralhealth/conditions/periodontal-disease.html

supports and holds the teeth in place, resulting in tooth loss. NIAMS-supported researchers found that administering a protein called tissue-nonspecific alkaline phosphatase to mice regulates the levels of phosphate and pyrophosphate, two molecules important in bone growth, restores the periodontal cementum (a substance which covers and protects the tooth's root), and promotes bone growth.[718] These findings expand our knowledge about the important balance of phosphate and pyrophosphate levels in restoring cementum growth. They also suggest that tissue-nonspecific alkaline phosphatase administration could be a generalized approach for regeneration of periodontal tissues in people.

From a throbbing tooth or aching jaw to a pounding migraine, pain in the oral and facial region, known as orofacial pain, afflicts five to twelve percent of the U.S. population.[719] Using an imaging technique to visualize pain signals in facial nerves, NIDCR researchers identified a protein called cyclin-dependent kinase 5 that enhances neurons' responses to painful stimuli. The scientists used fluorescence to track surges of pain signaling molecules in facial nerves, which flicker like twinkling lights in response to certain types of pain-related stimuli. Blocking the protein in mice blunted pain signaling.[720] The results could inform the development of safer, non-opioid pain therapies.

Regular visits to the dentist are essential for keeping our mouths healthy and keeping tooth decay and other problems at bay. However, studies show that most American adults do not visit a dentist regularly. This is especially true for those with limited incomes, a group disproportionately represented by Hispanic and non-Hispanic Black adults. In a study funded by NIDCR, expanding eligibility for public coverage of dental care was linked to reductions in racial and ethnic disparities in use of dental services. Despite lessened disparities, overall use of dental care remained low across racial and ethnic groups.[721] These findings demonstrate the importance of insurance coverage in equalizing access to dental care, but insurance remains one of multiple factors that could improve access to care.

Developed during 2018-2021 with extensive input from over 400 contributors, the report entitled, *Oral Health in America: Advances and Challenges,* was released in 2021 and examines 20 years of progress in oral health since the first Surgeon General's report on oral health in 2000.[722,723,724] The report articulated that NIDCR prioritized the science that places patients and people first, that alleviates the pain and discomfort from dental, oral, and craniofacial diseases, and that improves the quality of lives. The report was organized across the lifespan, characterized challenges and opportunities, and articulated a future vision and calls to action. The report is a living document that complements NIDCR's new Strategic Plan and that will help guide NIDCR over the next five years and beyond.[725]

---

[718] Nagasaki A, et al. *J Dent Res* 2021 Aug;100(9):993-1001. PMID: 33840251.
[719] https://www.nidcr.nih.gov/research/data-statistics/facial-pain
[720] Hu M, et al. *Cell Rep* 2022 Mar 8;38(10):110458. PMID: 35263573.
[721] Wehby GL, et al. *Health Aff (Millwood)* 2022 Jan;41(1):44-52. PMID: 34982622.
[722] https://www.nidcr.nih.gov/research/oralhealthinamerica
[723] Dye BA, et al. *Lancet* 2022 Jan 8;399(10320):127-128. PMID: 34951949.
[724] D'Souza RN, et al. *N Engl J Med* 2022 Mar 3;386(9):809-811. PMID: 35213102.
[725] https://www.nidcr.nih.gov/sites/default/files/2022-01/NIDCR-Strategic-Plan-2021-2026.pdf

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 because they most likely only have one faulty gene, which is not sufficient to cause disease. CF mainly affects the lungs, pancreas, liver, intestines, sinuses, and sex organs. It causes a person's mucus to become so thick and sticky that the mucus builds up in the lungs and blocks the airways. This buildup of mucus makes it easy for bacteria to grow, leading 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.[726] CF affects more than 30,000 Americans across all gender, racial, and ethnic groups. However, the disease is most common among White people of Northern European descent.[727] More than ten million Americans are carriers of a faulty CF gene, although many do not know it.

CF is caused by two faulty copies of a protein called cystic fibrosis transmembrane conductance regulator (CFTR), which spans the cell membrane and regulates the concentration of the chloride ion (one of the two components of sodium chloride, or table salt). The difference in salt concentrations between the inside of the cell and the outside are crucial to normal cell function. Thus, when CFTR is not working correctly, as in CF patients, it leads to dangerous mucus buildup in the lung. NHLBI has supported decades of basic research to understand the structure and function of CFTR with the goal of developing therapeutics to help CF patients live more normal lives. This work paved the way for industry development of ivacaftor, the first drug to treat the underlying cause of CF, approved by the FDA in 2012. More recently, NHLBI-supported clinical trials led to approval of a triple drug combination that improves lung function in about 90 percent of people with CF.[728,729]

Diabetes

Diabetes is the seventh leading cause of death in the U.S.[730] It is a disease that occurs when a person's blood glucose is chronically too high. Blood glucose is the body's main source of energy and comes from digesting food. Insulin, a hormone made by the pancreas, helps glucose from the blood stream into the cells to be used for energy. Sometimes the body does not make enough, or any, insulin, and sometimes it makes sufficient insulin, but the cells do not respond effectively to the insulin. Glucose then stays in the blood and does not reach the cells. More than 37 million Americans have diabetes, and another 96 million (or one in three people) have a condition called prediabetes, which puts them at elevated risk for developing diabetes.[731,732] Diabetes has serious health complications including heart disease, stroke, blindness, kidney failure, and lower-extremity amputations. The most common types of diabetes are type

[726] https://www.nhlbi.nih.gov/health/health-topics/topics/cf
[727] https://medlineplus.gov/genetics/condition/cystic-fibrosis/#inheritance
[728] Middleton PG, et al. *N Engl J Med* 2019 Nov 7;381(19):1809-1819. PMID: 31697873.
[729] Heijerman HGM, et al. *Lancet* 2019 Nov 23;394(10212):1940-1948. PMID: 31679946.
[730] https://www.cdc.gov/diabetes/basics/diabetes.html
[731] https://www.cdc.gov/diabetes/basics/diabetes.html
[732] https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html

1, type 2, and gestational diabetes. In people with type 1 diabetes, the body does not make insulin because 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 effectively. 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. Being overweight or obese is a significant risk factor for developing type 2 diabetes at any age. Gestational diabetes develops in some women when they are pregnant and needs to be managed to help prevent complications for the mother and neonate 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. 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.

Type 1 Diabetes Research

Type 1 diabetes occurs when the body's immune system mistakenly attacks and kills the insulin-producing beta cells of the pancreas. The NIDDK-supported Human Islet Research Network (HIRN), established in 2014, continues to pursue research in beta cell biology and replacement, advance understanding of how human beta cells are lost in type 1 diabetes, and develop innovative strategies for treatment, prevention, and monitoring.[733] For example, HIRN scientists used a sophisticated novel imaging technology, called imaging mass cytometry, to visualize the pancreas and gain new insights into how type 1 diabetes progresses, demonstrated in laboratory models how SARS-CoV-2infects certain human cells and tissues, including beta cells, and also discovered that SARS-CoV-2 infection directly induces changes in beta cells that could affect the course or onset of type 1 diabetes, and made significant progress toward developing new models of type 1 diabetes to study disease pathogenesis and to facilitate pre-clinical drug testing.

The NIDDK-led TrialNet is an international clinical trials network that conducts clinical trials to prevent clinical diagnosis of type 1 diabetes in high-risk individuals and to slow disease progression in newly diagnosed people.[734] TrialNet demonstrated that an immune-modulating therapy called teplizumab delayed the onset of clinical type 1 diabetes in high-risk individuals for at least three years, the first time that an early preventive treatment was shown to delay the onset of clinical type 1 diabetes.[735,736] TrialNet has two other ongoing prevention trials involving an immune-modulating drug called abatacept, and an immunosuppressive drug called hydroxychloroquine, as well as several planned trials. These trials require screening large numbers of people (over 200,000 to date) to identify those with autoimmune risk factors.

The Environmental Determinants of Diabetes in the Young (TEDDY) study is looking for the causes of type 1 diabetes. Supported by NIDDK, NIAID, NICHD, and NIEHS, TEDDY is a long-term study that enrolled over 8,000 newborns and is following them until they develop type 1 diabetes or turn 15 years of age, collecting

[733] https://hirnetwork.org/
[734] https://www.trialnet.org/
[735] Sims EK, et al. *Sci Transl Med* 2021 Mar 3;13(583):eabc8980. PMID: 33658358.
[736] Herold KC, et al. *N Engl J Med* 2019 Aug 15;381(7):603-613. PMID: 31180194.

dietary and health data as well as stool, blood, and other samples.[737] A significant omics effort is also under way to address questions related to the cause and course of autoimmunity and type 1 diabetes. Omics refers to the identification, quantification, and cataloging of every type of molecule within a certain classification group. For example, metabolomics identifies, quantifies, and catalogs all molecules involved in metabolism and proteomics does the same for proteins. Researchers are also studying the microbiome and virome—a collection of all bacteria and viruses living on and within the body. TEDDY researchers have uncovered important new details about how environmental factors affect the microbes in the gut (i.e., the gut microbiome) as children age, and how that could affect the risk of developing diabetes. Early findings suggest a protective effect of short-chain fatty acids in the early onset of type 1 diabetes.[738,739]

NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study have demonstrated that a short period of intensive glucose control early in life in those with type 1 diabetes prevents or delays complications of the heart, kidney, nerves, and eyes for decades. By analyzing biological samples from a subset of DCCT participants, scientists recently found signs of cardiac autoimmunity (when the body's immune system mistakenly attacks its own tissues, in this case the heart) in people who had type 1 diabetes and elevated blood glucose levels.[740] This work identified a novel CVD pathway specific to type 1 diabetes and further emphasized the importance of keeping blood glucose levels within a healthy range. In other research with DCCT/EDIC participants, researchers found that lower average blood glucose, fewer episodes of severe hypoglycemia, and lower blood pressure were each associated with better performance on cognition assessments.[741] These findings suggest that blood glucose control and blood pressure management could help to preserve cognitive function in people with type 1 diabetes as they age.

An artificial pancreas is a system made of three parts (a glucose monitor, a program to calculate how much insulin is needed, and an insulin infusion pump) that work together to mimic how a healthy pancreas controls blood glucose. They are one way to help people with type 1 diabetes manage their blood glucose levels.[742] NIDDK-supported research contributed to the development of the first commercially available hybrid artificial pancreas device approved by the FDA in 2016. Since then, NIDDK has contributed to the development or testing of many other new artificial pancreas devices. For example, positive clinical trial results led to FDA approval of the Control-IQ hybrid artificial pancreas device in both children and adults. Other clinical trial results showed that a next-generation artificial pancreas device outperformed a commercially available device in helping adolescents and young adults with type 1 diabetes keep their blood glucose levels in a healthy range.[743,744,745] Continued artificial pancreas research is important to give

[737] https://teddy.epi.usf.edu/
[738] Vatanen T, et al. *Nature* 2018 Oct;562(7728):589-594. PMID: 30356183.
[739] Stewart CJ, et al. *Nature* 2018 Oct;562(7728):583-588. PMID: 30356187.
[740] Sousa GR, et al. *Circulation* 2019 Feb 5;139(6):730-743. PMID: 30586738.
[741] Jacobson AM, et al. *Lancet Diabetes Endocrinol* 2021 Jul;9(7):436-445. PMID: 34051936.
[742] https://www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes/artificial-pancreas
[743] Brown SA, et al. *N Engl J Med* 2019 Oct 31;381(18):1707-1717. PMID: 31618560.
[744] Breton MD, et al. *N Engl J Med* 2020 Aug 27;383(9):836-845. PMID: 32846062.
[745] Bergenstal RM, et al. *Lancet* 2021 Jan 16;397(10270):208-219. PMID: 33453783.

people with type 1 diabetes (who range in age and have diverse needs) a variety of available devices so they can choose one that best fits their needs.

While artificial pancreas technology is a way to treat type 1 diabetes, a goal of type 1 diabetes research is to replace the destroyed pancreatic islets so that a person with the disease can produce insulin. Islet transplantation could thus be a strategy to treat some with type 1 diabetes. While studies on islet transplantation have generated promising results, it is still considered an experimental procedure and is not an FDA-approved treatment. Islet transplantation also currently requires chronic immunosuppression, which can have serious side effects, to avoid rejection of transplanted cells, and its long-term efficacy is still under investigation. The Clinical Islet Transplantation Consortium,[746] co-led by NIDDK and NIAID, played a large role in the 2021 decision by an FDA Advisory Panel to support future applications for the use of purified human pancreatic islet transplantation for treatment of patients with brittle type 1 diabetes.[747] Brittle type 1 diabetes is a more severe form of type 1 diabetes that is more difficult to control due to severe and frequent blood glucose swings from very low to very high levels. Although recent results have been very encouraging, more research is needed to achieve the goal of receiving FDA approval for islet replacement as a treatment option for people with type 1 diabetes.

Type 2 Diabetes Research

The Accelerating Medicines Partnership® (AMP®) program is a public-private partnership between the NIH, the FDA, and multiple public and private organizations.[748] Managed through the FNIH, AMP aims to identify and validate the most promising biological targets for therapeutics. In 2021, NIDDK expanded its successful AMP® Type 2 Diabetes program to include five additional metabolic diseases (liver diseases such as nonalcoholic steatohepatitis, kidney diseases, obesity, cardiovascular diseases, and type 1 diabetes) under a new program called AMP® Common Metabolic Diseases (CMD).[749,750] AMP® CMD will add substantial amounts of new data in the quest to better understand the genes and pathways that underlie these metabolic diseases and towards identifying new therapeutic targets.

Scientists demonstrated that genetic variation predicts individual responsiveness to the antidiabetic drug rosiglitazone. Rosiglitazone reduces insulin resistance (when cells do not respond to insulin) in type 2 diabetes, but its use is limited because some people experience significant side effects, including an increased risk of heart attack and stroke. In this study, a group of NIDDK-funded researchers developed a strategy to study the differential response to rosiglitazone and, in doing so, revealed genetic predictors of an adverse response to the drug.[751] Their findings suggest that it may one day be possible for clinicians to identify people who may benefit from rosiglitazone without adverse effects. The study also presents an approach to identify how human genetic variation determines response to a drug and may be an important tool for understanding drug responses in other diseases.

---

[746] https://www.citisletstudy.org/index.html
[747] Pullen LC. *Am J Transplant* 2021 Aug;21(8):2625-2626. PMID: 34352933.
[748] https://www.nih.gov/research-training/accelerating-medicines-partnership-amp
[749] https://hugeamp.org/
[750] https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/common-metabolic-diseases
[751] Hu W, et al. *Cell Stem Cell* 2019 Feb 7;24(2):299-308.e6. PMID: 30639037.

Genome-wide association studies aim to identify specific regions of DNA that may be associated with a trait, such as type 2 diabetes, by comparing the genetic variation in individuals with and without that trait (i.e., people with and without type 2 diabetes). However, the power of this approach to identify specific regions of DNA is directly linked to the number and diversity of people in the study—the more people and the greater diversity, the greater the power. NIDDK-supported researchers completed a pooled analysis of numerous previously conducted studies in Japan, China, Korea, and other East Asian countries, of a cumulative total of 433,540 participants, 77,418 of whom had type 2 diabetes. They identified 183 different parts of the genome where genetic features influence predisposition to type 2 diabetes in people with ancestry from this part of the world, increasing the total number of known genetic risk factors for type 2 diabetes by about 25 percent.[752] The findings have also reinforced and clarified previous discoveries in participants from other parts of the world and produced information that could eventually lead to new therapeutic approaches with the potential to benefit anyone with type 2 diabetes, regardless of their ancestry.

Most people with type 2 diabetes eventually need more than one medication to control blood glucose levels. A major challenge is to determine which of the many possible drugs is the best choice among people already treated with metformin, the most commonly used first-line type 2 diabetes drug. The Glycemia Reduction Approaches in Diabetes: An Effectiveness Study (GRADE), led by NIDDK with support from NHLBI, is comparing long-term benefits and risks of four widely used diabetes drugs in combination with metformin.[753,754] Preliminary data from more than 5,000 patients with type 2 diabetes have shown that liraglutide and insulin were the most effective of the four medications in keeping average blood glucose within an acceptable range. Data from comparative effectiveness trials similar to GRADE will help individuals with type 2 diabetes make informed decisions about how to best manage their conditions based on personal needs and the characteristics of the glucose-lowering medications.

There has been an increase in the number of children and teenagers with type 2 diabetes, primarily due to the obesity epidemic, which is the number one risk factor for developing type 2 diabetes. The NIDDK-supported Restoring Insulin Secretion (RISE) Pediatric Medication Study aims to determine if early, aggressive treatment can partially restore the capacity of the pancreas to secrete insulin in adolescents with prediabetes or early type 2 diabetes, and whether the enhancements could be preserved after treatment was withdrawn.[755] The RISE study produced sobering results; it did not identify a means to partially reverse pediatric type 2 diabetes. The study compared results in adults to those from youth treatment groups. Whereas the adults on treatment had improvements in parameters in pancreatic function, the results were not sustained after treatment ended. In youth, the parameters assessing pancreatic function declined with treatment and worsened after treatment ended.[756] These findings reinforce the continued, urgent need for new strategies to prevent and treat type 2 diabetes in youth.

---

[752] Spracklen CN, et al. *Nature* 2020 Jun;582(7811):240-245. PMID: 32499647.
[753] https://grade.bsc.gwu.edu/web/grade/home
[754] https://www.clinicaltrials.gov/ct2/show/study/NCT01794143
[755] https://rise.bsc.gwu.edu/web/rise
[756] Hannon TS, et al. *Pediatr Diabetes* 2020 Dec;21(8):1437-1446. PMID: 32985775.

The number of children, teenagers, and young adults with prediabetes or type 2 diabetes continues to increase in parallel with the rise in childhood obesity.[757,758] People with type 2 diabetes diagnosed during youth have a high risk of developing complications at an early age and are more likely than adults with the disease to develop multiple complications within 15 years after diagnosis. Complications were also more common among participants of racial and ethnic minority groups. These findings are from a follow-up study of the NIDDK-funded Treatment Options for Type 2 Diabetes in Adolescents and Youth clinical trial, which enrolled participants between 10 and 17 years old.[759] Since approved methods for treating pediatric type 2 diabetes are frequently ineffective, the results also underscore the critical need to identify better therapies for those who have the disease, as well as better prevention strategies for those at risk.

Over a third of all U.S. adults (96 million people) have prediabetes, and more than eight out of ten of them do not know they have it.[760] In a recent study, NIDDK-supported researchers found that community barbershops owned by Black individuals are promising venues for screening Black men for type 2 diabetes and identifying those with undiagnosed disease, so treatment can begin earlier. The researchers asked 895 Black men at eight different barbershops in Brooklyn, New York, if they would be willing to be screened for type 2 diabetes using a test that can be administered onsite and gives results in five minutes. About one-third of the men agreed to be screened and 290 were successfully tested. Of those, nine percent had undiagnosed type 2 diabetes and 28 percent had prediabetes.[761] Adopting strategies similar to the one in this study to help identify people with undiagnosed type 2 diabetes who would benefit from treatment, particularly if paired with approaches for lowering other barriers to obtaining proven therapies, hold promise to yield progress toward U.S. health equity.

Polycystic Ovary Syndrome (PCOS) is one of the most common causes of female infertility, affecting six to twelve percent of U.S. women of reproductive age. Women with PCOS are also often insulin resistant, meaning their bodies can make insulin but cannot use it effectively, increasing their risk for type 2 diabetes; more than half of women with PCOS develop type 2 diabetes by the age of 40.[762] NICHD-supported scientists tested blood and tissues from 18 women who had PCOS and 18 women who did not. The samples from women with PCOS revealed links between insulin resistance in fatty tissues, insulin resistance in the whole body, and higher levels of fatty acids and testosterone in the blood. The scientists discovered that the PCOS group had lower levels of a protein called GLUT-4 which is responsible for insulin-regulated uptake of glucose into fat and muscle cells from the blood stream. The results also showed and association between insulin resistance of body fat, and impaired function of the cells in the pancreas that produce insulin.[763] In the future, measuring insulin sensitivity in fat tissue could be a way to assess risk of metabolic syndrome and other health problems in women who have PCOS.

---

[757] https://www.cdc.gov/diabetes/data/statistics-report/newly-diagnosed-diabetes.html
[758] https://www.cdc.gov/diabetes/prevent-type-2/type-2-kids.html
[759] TODAY Study Group, Bjornstad P, et al. *N Engl J Med* 2021 Jul 29;385(5):416-426. PMID: 34320286.
[760] https://www.cdc.gov/diabetes/basics/quick-facts.html
[761] Osorio M, et al. *JAMA Intern Med* 2020 Apr 1;180(4):596-597. PMID: 31985740.
[762] https://www.cdc.gov/diabetes/basics/pcos.html
[763] Ezeh U, et al. *J Clin Endocrinol Metab* 2020 Jul 1;105(7):e2408-e2420. PMID: 32382742.

Air pollution may play a role in the development of cardiometabolic diseases, such as type 2 diabetes, with effects comparable to eating a high-fat diet. The effects were reversed when exposure to air pollution stopped. NIEHS-supported scientists compared three groups of mice: a control group that received clean air, a group exposed to air pollution, and a group that received clean air and was also fed a high-fat diet (high fat diets cause metabolic disease and type 2 diabetes in mice). Mice in both the air pollution and high-fat diet groups had insulin resistance and high blood glucose, both signs of prediabetes. Once air pollution was removed from the environment, mice showed improved metabolic health within a few months.[764,765] This study suggests that cardiometabolic health effects of air pollution are reversible, and if confirmed in humans, may have important implications for interventions to reduce air pollution.

It is widely known that our bones play additional roles in human physiology besides their main role as serving as our skeleton for support and movement. For example, bones secrete molecules into the blood that help regulate our metabolism, and when not signaling properly, can contribute to type 2 diabetes. NIAMS-supported researchers recently identified a factor secreted from bone cells, called DPP4, that impacts systemic energy metabolism. Its inhibition can lead to increased insulin synthesis and secretion and decreased glucose levels in the blood. This connection of bones with energy metabolism was also seen in type 2 diabetic patients who were treated with denosumab, an osteoporosis drug.[766] These results, if confirmed by further investigation, have important implications for future osteoporosis therapies because osteoporosis and diabetes are two common age-related conditions that often co-occur.

Gestational Diabetes Research

In June 2021, NIDDK established the Glycemic Observation and Metabolic Outcomes in Mothers and Offspring study (GO MOMs) to improve gestational diabetes screening and diagnosis by better understanding blood glucose levels throughout pregnancy.[767] The study aims to enroll about 2,150 women without diabetes in their first trimester of pregnancy and use continuous glucose monitoring technology to map blood glucose levels throughout pregnancy. GO MOMs builds on a previous NIH-funded landmark study of hyperglycemia and adverse pregnancy outcomes and its follow-up,[768] which found that women with elevated blood glucose during pregnancy, even if not high enough to meet the definition of gestational diabetes, are significantly more likely to develop type 2 diabetes or prediabetes years after pregnancy than their counterparts without elevated blood glucose. GO MOMs will build on these key findings by providing critical information to determine the timing and approach for future clinical trials to understand when and how to screen for and treat elevated blood glucose in pregnancy, and if this treatment will have any effect on children years later.

Clinical guidelines call for testing pregnant women for gestational diabetes during the 24th to 28th week of pregnancy.[769] However, new findings from NICHD-funded researchers suggest that the excess body fat seen in infants born to women with gestational diabetes is associated with higher maternal blood sugar

[764] Rajagopalan S, et al. *J Clin Invest* 2020 Nov 2;130(11):6034-6040. PMID: 32780721.
[765] https://factor.niehs.nih.gov/2020/10/papers/dert/index.htm#a3
[766] Weivoda MM, et al. *Nat Commun* 2020 Jan 7;11(1):87. PMID: 31911667.
[767] https://www.gomomsstudy.org/
[768] http://www.hapo.northwestern.edu/index.html
[769] ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. https://pubmed.ncbi.nlm.nih.gov/29370047/.

levels as early as the 10th week of pregnancy, which is long before the time when women are usually screened for the condition.[770,771] If the findings are confirmed, it could mean that women should be screened and treated for gestational diabetes as early as within the first three months of pregnancy.

Women who have had gestational diabetes during pregnancy have a greater chance of developing type 2 diabetes later in life. NICHD-funded researchers found that nine to sixteen years after pregnancy, women who had gestational diabetes have higher levels of liver enzymes associated with the accumulation of fat. Fat accumulation in the liver is a risk factor for insulin resistance and type 2 diabetes and could also place them at risk of liver damage and liver failure.[772,773] These findings suggest that gestational diabetes may serve as another risk factor for the early identification and prevention of liver fat accumulation in women in the years following pregnancy.

Identifying which women who develop gestational diabetes will go on to develop type 2 diabetes later in life would give doctors and patients sufficient time to take necessary steps to prevent the onset of type 2 diabetes. NICHD-funded researchers found that women who go on to develop type 2 diabetes after having gestational diabetes are more likely to have particular genetic profiles. In addition, the findings also suggest that a healthy diet may reduce the risk among women who have had gestational diabetes and are genetically susceptible to type 2 diabetes.[774,775] The findings provide insight into the genetic factors underlying the risk of type 2 diabetes and may inform strategies for reducing this risk among women who had gestational diabetes.

Cross-Cutting Diabetes Research

The SEARCH for Diabetes in Youth study, led by the CDC and NIDDK, found that the rates of type 1 and type 2 diabetes increased in people under the age of 20 in the U.S. from 2002 to 2015, with higher rates of increase among racial/ethnic minority youth. For type 1 diabetes, the scientists determined an overall rate of increase of 1.9 percent per year, with the steepest increases seen among Asian and Pacific Islanders (4.4 percent per year), Hispanics (4.0 percent per year), and Blacks (2.7 percent per year). Among youth with type 2 diabetes, the annual rate of increase in incidence was determined to be 4.8 percent per year, and the researchers observed the highest increases among Asian and Pacific Islanders (7.7 percent), Hispanics (6.5 percent), Blacks (6.0 percent), and American Indians (3.7 percent).[776,777] These trends are worrisome, as type 2 diabetes is more difficult to treat in youths than adults, and many youths with type 2 diabetes develop complications, meaning they could face the most serious burdens of the disease during their most productive years and for the rest of their lives.

---

[770] https://www.nichd.nih.gov/newsroom/news/030520-gestational-diabetes
[771] Li M, et al. *Lancet Diabetes Endocrinol* 2020 Apr;8(4):292-300. PMID: 32135135.
[772] https://www.nichd.nih.gov/newsroom/news/062819-gestational-diabetes
[773] Donnelly SR, et al. *J Diabetes* 2019 Nov;11(11):895-905. PMID: 31001915.
[774] https://www.nichd.nih.gov/newsroom/news/021320-gestational-diabetes
[775] Li M, et al. *BMJ Open Diabetes Res Care* 2020 Jan;8(1):e000850. PMID: 31958311.
[776] Divers J, et al. *MMWR Morb Mortal Wkly Rep* 2020 Feb 14;69(6):161-165. PMID: 32053581.
[777] https://searchfordiabetes.org/dspHome.cfm

The majority of diabetes cases can be classified as either type 1, type 2, or gestational diabetes; however, there are rarer forms such as brittle type 1 diabetes and ketosis-prone type 2 diabetes.[778] The NIDDK-supported Rare and Atypical Diabetes Network includes research efforts at 20 U.S. research institutions and aims to discover new forms of diabetes, understand what makes them different, and identify their causes.[779] Scientists plan to screen about 2,000 people with such unknown or atypical forms of the disease and will collect detailed health information from participants using questionnaires, physical exams, genetic sequencing, and other tests. These efforts will help provide a comprehensive description of the genetic and clinical characteristics of rare forms of diabetes, and underscore diabetes as a disease with many forms. Ultimately, the data may provide a framework to establish new diagnostic criteria for diabetes, find new markers for screening, or identify drug targets for new therapies that could ultimately bring precision medicine to diabetes.

Diabetic foot ulcers are a common and burdensome complication of diabetes and the leading cause of lower limb amputations in the U.S. The NIDDK-supported Diabetic Foot Consortium (DFC) is a multicenter clinical research network aiming to improve diabetic wound healing and prevent amputations among those with diabetes.[780] The DFC proposes to develop a biorepository that will collect and store biosamples and data from participants enrolled in current and future DFC studies. The DFC's first studies are focusing on characterizing diabetic foot ulcers and on finding biomarkers that can guide treatment and predict healing and recurrence. The consortium's long-term goal is to test new therapies for diabetic foot ulcers through clinical trials at an expanded number of clinical sites.

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 (heartburn more than twice a week) are common, while others such as genetic forms of liver disease are quite rare. Collectively, digestive diseases exact a significant toll on public health in terms of the 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 35 million visits to a doctor or emergency room in 2018 in the U.S. were due to diseases within the digestive system.[781] NIH's research spans the breadth of the many different digestive diseases affecting Americans, from investigating the diseases' biological and basic underpinnings to improving how they are treated and prevented.

Workshops, Meetings, and Symposiums to Advance Nutrition Research

Large scientific initiatives that bring together multidisciplinary, collaborative teams to answer difficult scientific questions and build the evidence base needed to develop new treatments, therapies, and clinical guidelines take years of planning. During 2017-2019, the NIH sponsored numerous nutrition-related scientific meetings, workshops, and symposiums. These events played a key role in the advancement of

[778] https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes
[779] https://www.atypicaldiabetesnetwork.org/
[780] http://diabeticfootconsortium.org/
[781] https://www.cdc.gov/nchs/fastats/digestive-diseases.htm

nutrition science by providing an opportunity to identify critical research gaps and scientific opportunities and disseminate research findings to the scientific community and to the public. A culmination of these meetings was the NIH Nutrition Research Report 2017-2019[782] that summarizes nutrition research and research training activities supported by NIH during this three-year period. The report was compiled by the ONR and shares the research directions of the 23 NIH institutes and centers supporting nutrition research.

Building on this report, NIH published the first NIH-wide strategic plan for nutrition research in May 2020, that emphasizes cross-cutting, innovative opportunities to advance nutrition research across a wide range of areas, from basic science to experimental design to research training. The 2020-2030 Strategic Plan for NIH Nutrition Research[783] was developed with extensive input from the broader external research community and the public. The Plan is organized around a unifying vision of precision nutrition research and includes four strategic goals and five cross-cutting research areas. These opportunities complement and enhance ongoing research efforts across NIH to improve health and to prevent or combat diseases and conditions affected by nutrition.

Precision nutrition research means that each of us has individualized, actionable dietary recommendations that help us decide what, when, why, and how to eat to optimize our health and quality of life. To help NIH realize this vision, the NIH Common Fund, in collaboration with the *All of Us* Research Program, awarded funding to clinics and centers across the country for a new study that will develop algorithms to predict individual responses to food and dietary routines. Nutrition for Precision Health (NPH), powered by the *All of Us* Research Program[784,785] will recruit and collect data from a diverse pool of 10,000 participants who are a part of the NIH's *All of Us* Research Program. The study team will use AI/ML to inform more personalized nutrition recommendations. NPH will be among the first ancillary studies of the *All of Us* Research Program and the NPH data will be integrated into the *All of Us* Researcher Workbench and made widely available to allow researchers to make discoveries that could improve health and prevent or treat diseases and conditions affected by nutrition.

Figure 22: Precision Nutrition Research Gaps and Opportunities Workshop Banner. Credit: NIH

[782] NIH Office of Nutrition Research. *NIH Nutrition Research Report 2017-2019*. 2020. https://dpcpsi.nih.gov/onr/nih-nutrition-report
[783] https://dpcpsi.nih.gov/onr/strategic-plan
[784] https://commonfund.nih.gov/nutritionforprecisionhealth
[785] https://www.nih.gov/news-events/news-releases/nih-awards-170-million-precision-nutrition-study

Although NIH is actively implementing the 2020-2030 Strategic Plan for NIH Nutrition Research and advancing Precision Nutrition research through the NPH program, it is already looking for the next areas of research to advance these ongoing efforts. In January 2021, NHLBI, NIDDK, and ODP convened a workshop on research gaps and opportunities.[786,787] Precision Nutrition research considers all of the variables that collectively work together with our diet to influence our health and quality of life: dietary habits, genetic background, health status, microbiome, metabolism, food environment, physical activity, socioeconomics, psychosocial characteristics, and environmental exposures. The workshop brought together scientists with diverse expertise to explore how best to address these complex factors. It also focused on diet-related chronic diseases, how AI/ML may be used to generate individualized dietary recommendations, and how to best prepare the next generation of future researchers to excel in and further advance the field of precision nutrition.

Figure 23: Precision Nutrition science infographic of the four strategic goals and five cross-cutting research areas of the Strategic Plan for NIH Nutrition Research. Credit: NIH

Enhancing Digestive Diseases Diagnostic Capabilities

Necrotizing enterocolitis (NEC) is a serious intestinal disease that often affects preterm infants. NEC is often not diagnosed until the conditions has reached a dangerous late stage. Scientists have been searching for ways to identify cases of NEC earlier, and especially for ways to identify NEC that can distinguish between NEC and other serious infections such as sepsis (when chemicals released in the bloodstream to fight an infection trigger damaging inflammation throughout the body). Both sepsis and NEC require a careful differential diagnosis, and both may be lethal if not diagnosed and treated appropriately. As the intestinal alkaline phosphatase (IAP) protein becomes more active early in the NEC disease process, NICHD-funded researchers assessed whether measuring IAP in the stool of infants could

[786] https://www.niddk.nih.gov/news/meetings-workshops/2021/precision-nutrition-workshop
[787] https://www.nhlbi.nih.gov/events/2021/precision-nutrition-research-gaps-and-opportunities-workshop

help signal early cases of NEC. They studied over 100 preterm infants in two hospitals in Louisiana and one hospital in Missouri. In this diagnostic study, high amounts of IAP protein in stool and low IAP protein activity were associated with diagnosis of NEC and may serve as useful biomarkers. These markers of IAP protein biochemistry were uniquely able to distinguish NEC from sepsis.[788]

The normal response to an infection or injury is for the body to activate its immune system, in which immune cells are sent to the site of infection or injury to kill what is causing the infection, such as bacterium, or to promote wound healing. Occasionally, the body sends out inflammatory cells when there is no infection or injury, leading to chronic inflammation which can damage healthy tissues. When chronic inflammation occurs in the intestinal track, it can lead to Crohn's disease or ulcerative colitis. Detecting intestinal inflammation early could allow doctors and patients to address the underlying cause before more serious conditions including Crohn's disease or ulcerative colitis occur. The RNA molecule is most associated with its role in helping cells translate the DNA code into a protein molecule that carries out a specific function, and collectively with all the other protein molecules, help determine how our bodies function. MicroRNAs are small pieces of RNA with a completely different function that is independent of translating DNA; they frequently serve as signaling molecules. NIAMS-supported researchers identified two microRNAs (miR-221 and miR-222) as important modulators of intestinal inflammation. Since microRNAs are relatively easy to detect, they may serve as a biomarker of immune response.[789] Further study is warranted to understand how effective these microRNAs will be as a potential biomarker of inflammation in patients with intestinal inflammation.

Biliary atresia is a rare and serious progressive liver disease diagnosed in infancy, for which an early surgical treatment can delay or prevent the need for liver transplantation. NIDDK-supported researchers in the Childhood Liver Disease Research Network (ChiLDReN)[790] identified a unique signature of gene activity levels at diagnosis that predicts survival in young children with biliary atresia—knowledge that could help determine disease progression and inform new treatment approaches.[791] Another network study identified gene variants present in infants with biliary atresia splenic malformation syndrome that may increase disease susceptibility.[792] In addition, an investigator-initiated study found that a two-step newborn screening approach measuring bilirubin levels could identify those with biliary atresia, which is progress toward a goal of more successfully diagnosing and treating babies earlier in the course of the disease.[793] ChiLDReN was renewed in FY 2019 to further advance research on liver diseases in children, including new studies of pediatric primary sclerosing cholangitis.[794,795]

[788] Heath M, et al. *JAMA Netw Open* 2019 Nov 1;2(11):e1914996. PMID: 31702803.
[789] Mikami Y, et al. *Immunity* 2021 Mar 9;54(3):514-525.e6. PMID: 33657395.
[790] https://childrennetwork.org/
[791] Luo Z, et al. *Gastroenterology* 2019 Oct;157(4):1138-1152.e14. PMID: 31228442.
[792] Berauer JP, et al. *Hepatology* 2019 Sep;70(3):899-910. PMID: 30664273.
[793] Harpavat S, et al. *JAMA* 2020 Mar 24;323(12):1141-1150. PMID: 32207797.
[794] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-501.html
[795] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-502.html

An estimated three million U.S. adults reported being diagnosed with inflammatory bowel disease (IBD) in 2015, and the occurrence of IBD has increased among older adults from 2001 to 2018.[796] Better understanding the causes of IBD could lead to more effective diagnostics and treatment. NIDDK-supported scientists identified changes caused by the community of microbes living in the gut that could contribute to IBD, including microbial metabolic byproducts (substances produced by microbes) and the human immune system's response. This pioneering research helped to more comprehensively characterize the metabolic and immune impacts of host-microbial interactions that contribute to IBD development.[797,798] These studies revealed potential new biomarkers to aid with diagnosis of IBD, and new targets for therapy. The infrastructure resources, results, and data were made available to researchers across the U.S. through the Inflammatory Bowel Disease Multi'omics Database[799] so that the broader research community can build upon the findings to further advance the field.

Developing New Treatments and Improving Outcomes of Current Treatments for Digestive Diseases

Liver cirrhosis is a condition in which the liver becomes scarred and permanently damaged. The scar tissue replaces healthy liver tissue and prevents the liver from working normally. As cirrhosis gets worse, the liver begins to fail, and a transplant is often the only available option to extend life. Liver cirrhosis has a wide variety of causes such as infection (chronic hepatitis C and chronic hepatitis B), poor diet (nonalcoholic fatty liver disease), unhealthy consumption of alcohol (alcoholic liver disease), and many others. Given the wide range of causes, NIDDK established the new Liver Cirrhosis Network[800,801] in partnership with NIAAA, to address alcoholic steatohepatitis, and NCI, to address liver cirrhosis as a major risk factor for liver cancer. The Liver Cirrhosis Network will advance clinical and translational research on cirrhosis of the liver in adults with a goal of improving the care of patients afflicted with this condition and a lessening the burden of cirrhosis disease complications.

Crohn's disease is a chronic disease that causes inflammation and irritation in the digestive tract and is estimated to affect over 500,000 people.[802] For one type of Crohn's disease, ileal Crohn's disease, only a subset of patients respond to clinical treatment, and scientists do not know why the therapy does not work for all patients. NIDDK-supported scientists identified a tell-tale combination of cells in people with ileal Crohn's disease who do not respond to one of its most effective treatments, which provided insights on the nature of the disease and may reveal new targets for therapy.[803] The results build upon previous findings that there are several distinct types of Crohn's disease, which could explain why treatment responses vary among those afflicted. These biological signatures could help health care providers predict which therapies would be most effective to treat their patients, and they could provide the basis for new treatments.

---

[796] https://www.cdc.gov/ibd/data-and-statistics/prevalence.html
[797] Lloyd-Price J, et al. *Nature* 2019 May;569(7758):655-662. PMID: 31142855.
[798] Franzosa EA, et al. *Nat Microbiol* 2019 Feb;4(2):293-305. PMID: 30531976.
[799] https://www.ibdmdb.org/
[800] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-003.html
[801] https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-20-004.html
[802] https://www.niddk.nih.gov/health-information/digestive-diseases/crohns-disease/definition-facts
[803] Martin JC, et al. *Cell* 2019 Sep 5;178(6):1493-1508.e20. PMID: 31474370.

Rotaviruses are the most common cause of diarrheal disease among infants and young children, and before vaccines, almost all U.S. children were infected with rotavirus before their fifth birthday. Rotaviruses still lead to more than 400,000 doctor visits and over 200,000 emergency room visits each year among U.S. children younger than five.[804] Rotavirus commonly causes severe, watery diarrhea and vomiting leading to dehydration and if not treated, can be fatal. An NIDDK-supported study of intestinal cells during rotavirus infection uncovered cellular signals that play a key role in causing severe disease even before damage to intestinal tissue is apparent.[805] These signals offer a potential therapeutic target for this common cause of diarrhea, dehydration, and death in children around the world.

Celiac disease is a chronic digestive and immune disorder that damages the small intestine. Research suggests that celiac disease only occurs in people who have certain gene variants and eat food that contains gluten. People who do not have these gene variants are very unlikely to develop celiac disease.[806] Celiac disease can cause long-lasting digestive problems and keep the body from getting all the nutrients it needs. NIDDK-supported researchers developed a new mouse model that mimics the immune system features and gluten-dependent intestinal damage seen in people with celiac disease.[807] This model provides a much-needed research tool, not only for helping to understand the biology of disease, but also for identifying new therapeutic targets and testing novel prevention and treatment strategies before they are tested in people.

Ulcerative colitis is a chronic IBD in which abnormal reactions of the immune system cause inflammation and ulcers on the inner lining of the large intestine. Research suggests that 600,000 to 900,000 people in the U.S. have ulcerative colitis.[808] Research supported by NIDDK made significant progress toward developing personalized therapeutic approaches for ulcerative colitis that consider the complex factors that drive the development of the disease in any given individual. The Predicting Response to Standardized Pediatric Colitis Therapy study, [809] supported by NIDDK, found that a combination of clinical, genetic, and immunologic tests can be used to predict response to standard medical therapy for children newly diagnosed with ulcerative colitis.[810] Another NIDDK-supported study found that high levels of a common fungus in the gut could signal whether a microbe-based treatment would be successful for people with ulcerative colitis.[811] These studies demonstrate the effectiveness of several therapeutic approaches for ulcerative colitis, especially when they are tailored to the individual.

Lipid nanoparticles (LNPs) are like tiny bubbles made of lipids (fats) that could potentially be used to deliver therapies to treat diseases and conditions. Two groups of NIDDK-supported scientists have tested LNPs in mouse models to deliver treatments for multiple forms of liver disease, including liver fibrosis,

[804] https://www.cdc.gov/rotavirus/surveillance.html
[805] Chang-Graham AL, et al. *Science* 2020 Nov 20;370(6519):eabc3621. PMID: 33214249.
[806] https://www.niddk.nih.gov/health-information/digestive-diseases/celiac-disease/symptoms-causes
[807] Abadie V, et al. *Nature* 2020 Feb;578(7796):600-604. PMID: 32051586.
[808] https://www.niddk.nih.gov/health-information/digestive-diseases/ulcerative-colitis/definition-facts
[809] Haberman Y, et al. *Nat Commun* 2019 Jan 3;10(1):38. PMID: 30604764.
[810] Hyams JS, et al. *Lancet* 2019 Apr 27;393(10182):1708-1720. PMID: 30935734.
[811] Leonardi I, et al. *Cell Host Microbe* 2020 May 13;27(5):823-829.e3. PMID: 32298656.

nonalcoholic fatty liver disease, and drug-induced liver injury.[812,813] Future studies will explore whether these new treatment approaches can be translated to the clinic to prevent liver disease progression and restore function in people.

The liver is the only major, internal organ that can regenerate, or produce new cells to replace those that were damaged. Better harnessing the liver's unique regenerative abilities could lead to more effective treatments for liver disease. NIDDK-supported research in mice identified which cells of the liver contribute in large part toward maintaining or regenerating the organ after injury. This work provides compelling evidence for the importance of cellular positioning within the zone 2 area of the liver lobule in maintaining equilibrium within the organ and replenishing it after injury.[814] Future studies could help to define the role of these cells in liver disease and inform therapeutic strategies to boost liver regeneration.

Research efforts by the Porphyrias Consortium,[815] supported by NIDDK and NCATS, and part of the NIH Rare Diseases Clinical Research Network, have led to the FDA-approval of breakthrough treatments for two forms of porphyria, a rare form of liver disease.[816] The studies helped map out the biological pathways involved in these disorders, paving the way for clinical trials sponsored by the pharmaceutical industry, with the participation of many consortium investigators and centers. In October 2019, FDA approved afamelanotide (Scenesse®) as the first agent available to help people with erythropoietic protoporphyria to experience pain-free sun exposure. In November 2019, FDA approved a drug called givosiran (Givlaari®), which improves the quality of life for people with acute intermittent porphyria.

Pancreatitis is inflammation of the pancreas, an organ near the stomach with two main functions: to make insulin and to make digestive enzymes to help digest food. Chronic pancreatitis is when the pancreas does not heal and gets worse over time, leading to lasting damage that can cause diabetes, cancer, or death. NIDDK, in partnership with NCI, continued support for the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer to conduct studies of people with chronic pancreatitis to improve understanding of disease processes and related outcomes, such as diabetes and pancreatic cancer, and to develop better means of diagnosis, treatment, and clinical management.[817] As part of the Consortium, NIDDK and NCI supported an expanded iteration of a pediatric pancreatitis research network called the International Study Group of Pediatric Pancreatitis: In Search for a Cure, which is characterizing the acute recurrent and chronic forms of pediatric pancreatitis.

Irritable bowel syndrome (IBS) is a group of symptoms that occur together, including abdominal pain and changes in bowel movements, such as diarrhea, constipation, or both. Children with IBS also often experience anxiety and depressive symptoms associated with pain severity. NINR-supported researchers examined the relationship between these psychological symptoms and the processes of somatization

[812] Hu M, et al. *Nat Nanotechnol* 2021 Apr;16(4):466-477. PMID: 33495618.
[813] Rizvi F, et al. *Nat Commun* 2021 Jan 27;12(1):613. PMID: 33504774.
[814] Wei Y, et al. *Science* 2021 Feb 26;371(6532):eabb1625. PMID: 33632817.
[815] https://www1.rarediseasesnetwork.org/cms/porphyrias/
[816] https://ncats.nih.gov/pubs/features/rdcrn-porphyrias-consortium
[817] https://www.dmscro.org/cpdpc

(experiencing physical symptoms that cannot be explained medically) and pain catastrophizing (expecting the worst and feeling helpless in response to pain). They found that in children with IBS, somatization and pain catastrophizing influence the relationship between anxiety and depressive symptoms and pain severity.[818] These findings suggest that treating somatization and pain catastrophizing could alleviate abdominal pain more effectively than treating anxiety and depressive symptoms in children with IBS.

Intestinal Stem Cells are Crucial for a Healthy GI Track

The absorptive and protective functions of the intestine depend in part on the intestinal epithelium (physical and biochemical barrier separating the host tissue from bacteria and food inside intestine), which requires continual turnover to function—cells are lost at the surface and replaced from stem cells at the base. However, in diseased or inflamed conditions, the epithelium may not be renewed at the pace needed to maintain a barrier against the potentially harmful contents of the digestive tract, leading to disease. Thus, the ability of intestinal stem cells to heal and maintain the epithelial barrier is essential to maintain normal function of the intestine. NIDDK, together with NIAID, continue to support the Intestinal Stem Cell Consortium,[819] established in 2009, to stimulate basic research through developing new technologies to isolate, characterize, cultivate, and manipulate intestinal stem cells. The consortium was renewed in FY 2019 to continue its work advancing understanding of intestinal epithelial stem cell biology with the ultimate goal of developing novel therapies targeting these stem cells and their supportive niche to regenerate and rebuild the human intestine.[820]

Intestinal stem cells do not just become mature intestinal epithelial cells without help from other cells in and around the intestine. Better understanding how these different cells interact could lead to new ways to diagnose, treat, or prevent the onset of intestinal diseases. NIDDK-supported researchers discovered that intestinal stem cells interact with nearby immune cells in a bi-directional manner that affects both the renewal of this stem cell source and remodeling of the intestinal lining during infection. This research demonstrated the importance of this crosstalk between cell types for maintaining the stem cell pool and healthy intestinal lining in both healthy and infected states.[821]

Better Understanding Risk Factors for Digestive Diseases

IBD is an umbrella term used to describe disorders that cause chronic inflammation of the GI tract, of which the two most common forms are Crohn's disease and ulcerative colitis. The NIDDK IBD Genetics Consortium[822] is a major driver of the Institute's research program on the role of genetic factors in the development of Crohn's disease and ulcerative colitis. The consortium is part of an international IBD genetics consortium that has aided in increasing the power of genomic analyses to enable discovery of additional risk gene variants for IBD. Recent studies from consortium investigators have shed light on how

[818] Hollier JM, et al. *Neurogastroenterol Motil* 2019 Feb;31(2):e13509. PMID: 30549152.
[819] https://iscconsortium.org/Information
[820] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-507.html
[821] Biton M, et al. *Cell* 2018 Nov 15;175(5):1307-1320.e22. PMID: 30392957.
[822] https://ibdgc.org/

known genetic risk factors can contribute to Crohn's disease and treatment response,[823] opening the door to new diagnostics and treatment approaches.

NAFLD is a condition in which excess fat builds up in the liver, disrupting normal function, and if left untreated, could lead to T2D, cirrhosis, or liver cancer. Experts estimate that about 24 percent of all U.S. adults have NAFLD, including 75 percent of people who are overweight and over 90 percent of people with severe obesity.[824] NIDDK-supported researchers discovered that consuming high amounts of fructose may promote NAFLD by damaging the intestinal barrier, leading to inflammation and other effects on the liver.[825] Fructose is a common type of sugar in the American diet, including in its processed form called high-fructose corn syrup that is used to sweeten a variety of foods and beverages. The findings from this study could lead to new ways to treat and prevent NAFLD, which affects an increasingly large portion of the U.S. population.

The microbiome is the collection of all microbes, such as bacteria, fungi, viruses, and their genes, that naturally live on and inside our bodies, especially inside our GI track, that are vital to human health and wellness. For example, they protect us against pathogens, help our immune system develop, and enable us to digest food to produce energy. Although beneficial and crucial for survival, it is also necessary for the body to limit where and how these microbes can live. The GI track secretes a layer of mucus to separate the microbiota from the body's intestinal tissues. NIDDK-supported research using a mouse model has provided a new understanding of how mucus coating the inner colon isolates bacteria from the gut wall, potentially offering new ways to diagnose and treat intestinal inflammation.[826] This study suggests that the fecal mucus coating could serve as a diagnostic tool to detect gastrointestinal disease, and, ultimately, as a target for new approaches to restore the gut to a healthy state.

Research and Resources to Reduce Drug-Induced Liver Injury

Drug-induced liver injury (DILI) is one of the most common causes of acute liver failure in the U.S. and is one of the most frequent obstacles in the development and approval of new drugs. Most drugs, especially those taken orally, must pass through the liver (the primary site for drug metabolism) before traveling throughout the rest of the body. This makes the liver particularly susceptible to injury from a dangerously high dose of drug or the wrong combination of drugs. Through a collaboration between NIDDK's Drug-Induced Liver Injury Network and the International DILI Consortium, researchers found that people with a genetic variant implicated in autoimmune diseases, called *PTPN22*, are at increased risk of liver injury triggered by drugs.[827] This study opens the door for developing therapies for DILI that focus on improving the activity of PTPN22 and the related cellular pathways that curb immune responses.

In addition to supporting research to answer unknown questions on DILI, NIH also provides public resources that consolidate and disseminate information so doctors and patients can make better decisions in managing their health. NIDDK, in conjunction with NLM, continues to support the *LiverTox*

[823] Nayar S, et al. *Nature* 2021 May;593(7858):275-281. PMID: 33789339.
[824] https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts
[825] Todoric J, et al. *Nat Metab* 2020 Oct;2(10):1034-1045. PMID: 32839596.
[826] Bergstrom K, et al. *Science* 2020 Oct 23;370(6515):467-472. PMID: 33093110.
[827] Cirulli ET, et al. *Gastroenterology* 2019 May;156(6):1707-1716.e2. PMID: 30664875.

website.[828] This website provides information on DILI resulting from prescription and over-the-counter drugs, herbal products, and dietary supplements. The website serves as a public resource to aid health care providers in diagnosing, and investigators in studying, liver injury due to drugs and herbs/supplements.

Eye Diseases and Disorders of Vision

Diseases and disorders of the eye affect millions of Americans and create a significant burden for those afflicted, and for society at large. More than 4.2 million Americans over the age of 40 have low vision or are legally blind.[829] Age-related macular degeneration (AMD), which results in damage to sharp and central vision and is a leading cause of blindness, affects 1.8 million Americans, with another 7.3 million at risk for developing AMD.[830] Cataracts, another common and burdensome disorder, results in clouded vision and is the leading cause of blindness across the world. In the U.S., more than 20 million Americans over the age of 40 are estimated to have cataracts in one or both eyes. In fact, vision loss ranks among the top ten causes of disability in the U.S., and as the population of older people continues to increase, the number of people experiencing vision loss will continue to increase.[831] These and many other common ocular diseases and disorders, such as glaucoma and diabetic retinopathy, are part of NIH's broad ocular research portfolio, led by NEI. Additional updates related to neural degeneration in eye diseases are presented in the Neuroscience section of this chapter.

Understanding Prevalence, Risk Factors, and Underlying Biology

Dry eye disease, often related to inflammation and impaired tear production, is a painful yet common condition for which there are few effective treatments, and when left untreated, may lead to vision loss. The highest density of nerves in the body are found in the cornea, the transparent layer at the front of the eye. NEI launched the Anterior Segment Initiative in 2019 to understand inflammation and pain in the eye and to study pathways of dry eye, ocular pain and itch, corneal nerve innervation, the sparse microorganisms on the surface of the eye (ocular microbiome), and underlying immune factors.[832] This research will provide foundational work to develop treatments for dry eye disease, which disproportionately impacts women, and other inflammatory conditions that lead to vision loss.

In many common eye diseases, the cells that receive light, called photoreceptors, are damaged, leading to blindness even if the remaining neural circuitry is intact. NEI scientists have shown that by inserting light-sensitive proteins, called opsins, into other types of neurons in the retina (bipolar cells or ganglion cells), they are able to introduce light-sensitivity in blind mice, even if the photoreceptors are non-functioning.[833] Research teams have been bioengineering faster and more sensitive opsin activity to

[828] National Institute of Diabetes and Digestive and Kidney Diseases. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. 2016. https://www.ncbi.nlm.nih.gov/books/NBK548162/
[829] https://www.cdc.gov/visionhealth/basics/ced/.
[830] https://www.cdc.gov/visionhealth/basics/ced/.
[831] https://www.cdc.gov/visionhealth/basics/ced/
[832] www.nei.nih.gov/about/goals-and-accomplishments/nei-research-initiatives/anterior-segment-initiative
[833] https://www.nei.nih.gov/about/news-and-events/news/scientists-use-gene-therapy-and-novel-light-sensing-protein-restore-vision-mice

restore visual functions.[834,835,836] This foundational research has led to a phase 2b clinical trial in adults with retinitis pigmentosa, an inherited form of retinal degeneration that kills photoreceptors.

Stem cells are the cells that develop into blood, brain, bones, and all of the body's organs. They have the potential to repair, restore, replace, and regenerate cells, and could possibly be used to treat many medical conditions and diseases, such as those affecting the eye. Stem cells collected from bone marrow have been shown to repair tissue and reduce scarring in the cornea of the eye; they have been studied as a possible treatment for a wide range of human diseases due to their regenerative properties.[837] The Regenerative Medicine Innovation Project, a recently launched clinical trial led by NEI and funded through the 21st Century Cures Act, is investigating restorative factors secreted by these stem cells to create a therapeutic eye drop to accelerate corneal wound healing.[838] In another project, NEI scientists found that exosomes secreted from bone marrow stem cells were able to preserve retinal ganglion cells (RGCs) after injury.[839] Exosomes are small extracellular vesicles secreted by cells into the body and are thought to be a form of cell-cell communication. They are filled with cellular fragments including genetic messages (e.g., RNA), proteins, and other constituents. Damage to RGCs can lead to glaucoma, a leading cause of blindness. The ingredients within the exosome are giving researchers ideas on how to treat glaucoma more effectively by manipulating these components within the exosome.[840]

The NEI Audacious Goals Initiative (AGI) is an effort to restore vision by regenerating the retina, the light-sensitive tissue in the back of the eye.[841] AGI aims to regenerate neuronal function in the retina and optic nerves damaged in patients with blinding diseases like glaucoma and AMD. AGI created three research consortia that share data and methodologies to support the following goals: to identify neuro-regenerative factors, to develop animal models that better reflect human disease, and to create novel imaging techniques, such as a technique called diffusion basis spectrum imaging, to image optic nerve function in patients with glaucoma and multiple sclerosis.[842,843,844]

The cornea, the transparent outer surface of the eye, is prone to damage from environmental exposures. NEI scientists have shown that by increasing the proliferative abilities of cells in the cornea, they were able to rebuild damaged corneas from four patients who experienced chemical burns.[845] This procedure used stem cells derived from the patient's healthy eye to transplant into the damaged eye and is the first

[834] www.the-scientist.com/news-opinion/optogenetic-manipulations-create-perception-without-sensory-input-66171
[835] Berry MH, et al. *Nat Commun* 2019;10(1):1221. PMID: 30874546.
[836] Batabyal S, et al. *J Biophotonics* 2021;14(1):e202000234. PMID: 33026157.
[837] Elhusseiny AM, et al. *Stem Cells Transl Med* 2022;11(3):259-268. PMID: 35303110.
[838] Putra I, et al. *Transl Vis Sci Technol* 2021;10(10):3. PMID: 34383879.
[839] Mead B, et al. *Exp Eye Res* 2020;197:108071. PMID: 32574667.
[840] Mead B, et al. *Cells* 2021;10(7):1564. PMID: 34206213.
[841] https://www.nei.nih.gov/about/goals-and-accomplishments/nei-research-initiatives/audacious-goals-initiative
[842] Becker SM, et al. *Ocul Pharmacol Ther* 2021;37(3):144-146. PMID: 32877259.
[843] Becker SM, et al. *Transl Vis Sci Technol* 2021;10(10):2. PMID: 34383880.
[844] Vavasour IM, et al. *Mult Scler* 2022:28(3):418-428. PMID: 3413216.
[845] https://www.newswise.com/articles/mass-eye-and-ear-doctors-collaborate-with-dana-farber-to-rebuild-damaged-corneas-using-patients-own-stem-cells-for-first-time-in-united-states

of its kind to occur in the U.S. Researchers will build upon this groundbreaking study and further improve the procedure to move it closer towards FDA approval as a new therapy for restoring vision.

Patients with stroke damage to the brain's visual cortex often have a poor prognosis for recovering visual function. NEI researchers were able to demonstrate that some visual capabilities remain immediately after the stroke occurs, but that they degrade over time. Capitalizing on these observations, they found that patients that received early training interventions and vision rehabilitation within the first three months of stroke occurrence showed improved motion discrimination and light detection faster and more efficiently than patients receiving treatment after six months.[846] These findings suggest there is hope for people recovering some vision following a stroke if they receive immediate and proper visual therapy.

An international collaboration including the NEI Glaucoma Human Genetics Collaboration Consortium analyzed genes in over 34,000 people with glaucoma from European, African, and Asian descent, identifying 44 new gene locations and confirming 83 previously identified ones.[847] While earlier studies had primarily focused on European descent, the cross-ancestry comparison found most genes were consistent across groups.[848] Similarly, an international collaboration in Mexico, Pakistan, and the U.S. conducted whole-genome sequencing of a diverse population of 409 individuals from families with rare, inherited retinal dystrophies to identify 42 new disease-causing gene variants and confirm 52 others.[849] These results—identification of around 86 new gene locations potentially involved in eye diseases and disorders—lay the foundation for identifying new drug targets in the future to help prevent or restore vision loss.

The Eyes of Africa Project is an international collaborative of researchers that examines the genetic, economic, societal, and personal effects of vision loss in Africa.[850] Since individuals of African descent are four times more susceptible to primary open angle glaucoma (POAG), have a higher chance of going blind, and present with the disease at earlier ages then those of European or Asian descent, it is critical to define the disease in this population in order to understand these disparities.[851] Researchers found a genetic association between POAG and a region of the genome called *APBB2* that was observed only in individuals of African ancestry. Importantly, the risk associated with the *APBB2* region appeared not to be mediated by increased intraocular pressure or measures of optic nerve neuropathy, risk factors that are key clinical indicators for the disease.[852] Thus, this study suggests not only a new insight to POAG disease pathogenesis but a potential diagnostic tool.

Retinoschisin (RS1) is a protein required for proper organization of the retina in the eye, and defects have been associated with a condition that affects the vision called X-linked retinoschisis (XLRS).[853] A recent

---

[846] Saionz E, et al. *Brain* 2020;143(6):1857-1872. PMID: 32428211.
[847] https://masseyeandear.org/news/press-releases/2021/02/international-team-identifies-127-glaucoma-genes-in-largest-study-of-its-kind
[848] Gharahkhani P, et al. *Nat Commun* 2021:12(1):1258. PMID: 33627673.
[849] Biswas P, et al. *PLoS Genet* 2021;17(10):e1009848. PMID: 34662339.
[850] https://h3africa.org/index.php/consortium/adeyinka-ashaye/.
[851] Hauser MA, et al. *JAMA* 2019;322(17):1682-1691: PMID: 31688885.
[852] Olawoye O, et al. *BMC Ophthalmol* 2021;21(1):272. PMID: 34243759.
[853] Heymann BJ, et al. *J Cell Biol* 2019;218(3):1027-1038. PMID: 30630865.

analysis developed a molecular model that allows the specific locations within the mutated RS1 protein to be mapped and their impact on the protein's structure to be defined. Researchers also observed that, under certain conditions, isolated RS1 assembles into long filaments with branches. This suggests that RS1-filament networks could form a bridge between cells in the retina. Future studies will test this hypothesis by visualizing RS1 within the mouse retina in sufficient detail to detect such filaments, if present.

In most cases, glaucoma is caused by an increase in intraocular pressure, which is largely regulated by an eye tissue known as the trabecular meshwork. A protein that regulates gene expression called GLIS1 is associated with glaucoma in humans and the regulation of intraocular pressure inside the eyes.[854] Researchers found that mice lacking GLIS1 developed enlarged eyes and a long-lasting increase in intraocular pressure. This study sheds light on the cellular and molecular causes of the second most common cause of blindness in the U.S. and may lead to the development of new therapies.[855]

Improving Treatment and Prevention

Gene therapy is a technique that modifies a person's genes to treat or cure disease, for example, by replacing a disease-causing gene with a healthy copy of the gene. A number of eye diseases have benefited from gene therapies where DNA coding for therapeutic proteins is delivered to cells in the eye. Current therapies deliver the DNA using viral transporters, but this method has limitations, including the development of an immune response against the viral carrier and limits to the size of gene that will fit in the virus. NIBIB-funded researchers have created nanoparticles for successful gene therapy of a mouse model of macular degeneration.[856] The nanoparticle carriers have the potential to significantly expand the effectiveness of gene therapies for human eye diseases, including blindness.

Investigators supported by NIA and NEI used a novel technique to restore vision lost to age and disease in mice.[857] By using epigenetic approaches (activating or deactivating genes without changing the underlying genetic sequence) the investigators were able to rejuvenate damaged retinal cells, protect the optic nerve, and reverse vision loss in a mouse model of glaucoma. Refining a technique that won a Nobel prize in 2012, the researchers used a harmless virus to introduce just a few genes that can reprogram the DNA of mature cells to transform them back into young stem cells.[858] Stem cells can regenerate function lost to age, illness, or injury, but mature cells cannot. In previous studies, this technique triggered rapid cell growth and tumor development, but these investigators found a way to keep the beneficial effects and eliminate the dangerous ones by leaving out one of the four genes, called *MYC*, which is closely related to cancer and can shorten the lifespan of mice. While these results are encouraging, epigenetic reprogramming is complex, and additional research is needed before this therapy can be used safely in humans.

---

[854] https://factor.niehs.nih.gov/2021/10/papers/dir/index.htm#a3.
[855] Nair KS, et al. *Nat Commun* 2021;12(1):4877. PMID: 34385434.
[856] https://www.nibib.nih.gov/news-events/newsroom/nanoparticles-enhance-gene-therapies-eye-disease.
[857] https://www.nia.nih.gov/news/gene-therapy-techniques-restore-vision-damage-age-and-glaucoma-mice.
[858] https://www.nobelprize.org/prizes/medicine/2012/press-release/

Many chronic eye diseases require close monitoring of patients, often through digitized ocular imaging, which allows researchers to accumulate large amounts of data that track disease progression over time. Pairing these images with clinician's diagnoses, researchers can train AI algorithms to screen for a number of diseases. This technology has the potential to improve the speed, accuracy, efficiency, and objectivity of diagnoses and facilitate earlier detection and disease progression in patients. NEI researchers developed AI to screen for retinopathy of prematurity (ROP), a leading cause of childhood blindness resulting from abnormal blood vessel growth in premature, low birthweight infants.[859,860] This proof-of-concept study showed that AI technology identified ROP at a higher rate than trained ophthalmologists.[861]

NEI researchers launched a clinical trial to test the safety of a novel patient-specific stem cell-based therapy to treat geographic atrophy, the advanced "dry" form of AMD.[862] The protocol, which prevented blindness in animal models, is the first clinical trial in the U.S. to use replacement tissues from patient-derived stem cells. The preclinical research for the trial was supported by the NEI Intramural Research Program and by an NIH Common Fund Therapeutic Challenge Award.[863,864] The trial is being conducted at the NIH Clinical Center in Bethesda, MD. Should early safety be confirmed, later study phases will include more patients to assess the efficacy of the implant to prevent blindness and restore vision in patients with geographic atrophy.

The age-related Macular Degeneration Integrative Biology Initiative is a new collaborative initiative to discover the underlying pathology of AMD by studying stem cells derived from AMD patient retinal cells.[865] NEI has partnered with the New York Stem Cell Foundation to facilitate drug discovery and other basic research efforts by creating a database of genetic and clinical information from a cohort of AMD patients carrying high prevalence risk alleles, or segments of DNA known to increase risk for developing AMD. The scientific community can compare genetic background and deidentified patient medical history with biochemical studies using stem cell lines derived from the AMD patients.

Many of the leading causes of vision are preventable if caught and treated early. Lack of awareness about vision health leads to many patients going blind from preventable diseases. NEI's National Eye Health Education Program (NEHEP) is actively engaging the community to bring awareness to vision health. For example, NEHEP's Write the Vision program focuses on bringing eye health messages specifically to African American communities and health professionals working in African American communities,[866] and

[859] https://news.ohsu.edu/2020/01/30/tech-that-detects-cause-of-preemie-blindness-gets-federal-nod
[860] https://www.nei.nih.gov/about/news-and-events/news/ai-may-help-spot-newborns-risk-most-severe-form-blinding-disease.
[861] Greenwald MF, et al. *J AAPOS* 2020;24(3):160-162. PMID: 32289490.
[862] https://www.nih.gov/news-events/news-releases/nih-launches-first-us-clinical-trial-patient-derived-stem-cell-therapy-replace-dying-cells-retina
[863] https://commonfund.nih.gov/stemcells
[864] Sharma R, et al. *Sci Transl Med* 2019;11(1475):eaat5580. PMID: 30651323.
[865] https://www.nei.nih.gov/about/goals-and-accomplishments/nei-research-initiatives/regenerative-medicine/amd-integrative-biology-initiative
[866] www.nei.nih.gov/learn-about-eye-health/outreach-campaigns-and-resources/eye-health-among-african-americans

the *¡Ojo con su visión!* pilot[867] raises awareness about eye health among Hispanic/Latino adults. NEHEP also released two *Talk with Your Doctor* guides, one for Glaucoma[868] and one for AMD,[869] to encourage meaningful conversations between doctors and their patients with glaucoma and AMD.

NEI's communications office coordinated a video shorts campaign for 2020 called More than Meets the Eye. The YouTube series features a spectrum of research funded by the Institute, such as A New Device Helps Treat Dry Eye,[870] Finding Better Ways to Treat Eye Diseases and Vision Disorders,[871] Reversing the Course of Vision Loss,[872] Research to Prevent Lens Detachment,[873] and How the Zebrafish Could Help Us Treat Eye Disease.[874] The video shorts were targeted to the public to better inform them about the value of basic and translational research and the importance of not neglecting their vision health.

Two successful Age-related Eye Disease (AREDS) intervention trials, AREDS1 and AREDS2, for AMD demonstrated the benefits of dietary supplements in reducing progression to late-stage disease.[875] Building on these results and to incorporate the most recent scientific findings, in March 2020, NEI hosted experts in a nutrition workshop that focused on B vitamins and very long chain fatty acids, which may impact the progression of AMD. NEI is now planning an AREDS3, a clinical trial of dietary supplements to possibly prevent progression in earlier stages of AMD.

Technology Development

During the COVID-19 pandemic, telemedicine gained more prominence and acceptance as an alternative to in-person doctor's visits. Vision researchers, who rely heavily on imaging for diagnosing and establishing medical care, were able to adapt by integrating AI-based devices into their medical practice. Two recently FDA-approved AI-based devices are reducing the need for regular doctor visits by allowing doctors to make highly personalized decisions about medical care without seeing the patient in person. EyeArt is a tool that accurately screens for early to mild stages of diabetic retinopathy and can be deployed in telehealth settings,[876,877] and Notal Vision is a remote patient monitoring service that uses AI to monitor AMD progression.[878,879] These devices are transforming the ways clinicians diagnose eye diseases and improve the quality of life for patients.

---

[867] www.nei.nih.gov/nehep/programs/ojo
[868] www.nei.nih.gov/TalkWithYourDoctorGlaucoma
[869] www.nei.nih.gov/TalkWithYourDoctorAMD
[870] https://www.nei.nih.gov/about/news-and-events/news/penn-engineerings-blinking-eye-chip-used-disease-modeling-and-drug-testing
[871] https://www.youtube.com/watch?v=EAX5Np8T1OY
[872] https://www.youtube.com/watch?v=eG0rcITxVOA
[873] https://www.youtube.com/watch?v=_Lb_CC35bo4
[874] https://www.youtube.com/watch?v=QDSuYWILJds
[875] https://www.nei.nih.gov/about/news-and-events/news/nih-study-provides-clarity-supplements-protection-against-blinding-eye-disease
[876] https://www.eyenuk.com/us-en/products/eyeart/
[877] Bhaskaranand M, et al. *Diabetes Technol Ther* 2019;21(11):635-643. PMID: 31335200.
[878] https://www.nei.nih.gov/about/news-and-events/news/patients-use-device-monitor-amd-home
[879] Keenan TDL, et al. *Ophthalmology Science*. Volume 1, Issue 2, June 2021. www.sciencedirect.com/science/article/pii/S2666914521000324

The eye's transparency has allowed doctors to easily photograph the retina, located at the back of the eye, to assess its health. Revolutionary tools such as Optical Coherence Tomography (OCT) now provide 3D cross-sectional images of deep layers of tissue to examine tissue thickness and identify leaky blood vessels, which informs treatment decisions in real time.[880] This non-invasive imaging technique can also be used to examine blood vessels running through different areas of the eye, which has improved diagnosis of vision and neurologic disease. NEI researchers also developed handheld, portable OCT imagers, which make eye imaging accessible to a larger number of patients, including infants and those who are bedridden.

Smartphone GPS navigation systems have been useful for visually impaired individuals in open spaces, but current GPS features of cell phones are inaccurate in indoor settings. Using computer vision technologies, researchers are creating a smartphone-based indoor navigation app to estimate the user's location in an indoor environment and guide them to a desired destination.[881,882] The new navigation app runs on a standard smartphone and requires no new physical infrastructure as it utilizes existing signage. This app supports the user to walk freely with the smartphone as their guide without having to actively search for signs with the smartphone, which is often challenging for people with severe visual impairments.

Kidney Diseases

The kidneys (two bean-shaped organs about the size of a fist) filter extra water and waste 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.[883] More than one in seven U.S. adults suffer from kidney diseases, including chronic kidney disease (CKD), which affects an estimated 37 million adults.[884] 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.

Understanding Kidney Biology to Inform New Treatments and Clinical Guidelines for Kidney Diseases

A growing consensus suggests that CKD and acute kidney injury (when the kidneys suddenly stop working properly, usually as a complication of another serious illness) are diverse disorders that can be categorized into specific subgroups, each of which is driven by different disease pathways. Thus, a better understanding of the causes and features of the different subtypes can lead to the development of more effective, individualized treatment options. To accomplish this, NIDDK established the Kidney Precision Medicine Project, which aims to ethically obtain and evaluate human kidney biopsies from participants with acute kidney injury or CKD, create a kidney tissue atlas, define disease subgroups, and identify critical

[880] https://www.ohsu.edu/casey-eye-institute/innovations-2022-advancing-ocular-imaging
[881] https://www.youtube.com/watch?v=fjok-fMIx-8&feature=youtu.be
[882] https://www.ski.org/sites/default/files/publications/fusco-coughlan-v2.pdf
[883] https://www.niddk.nih.gov/health-information/kidney-disease
[884] https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html

cells, pathways, and targets for novel therapies.[885,886,887,888] Additional technology development will be supported by small business programs.

There is no cure for CKD and it can get worse over time. CKD may eventually lead to kidney failure, requiring a kidney transplant or repeated blood-filtering treatments called dialysis. Although more common in the elderly, CKD occurs in kids and young adults for many reasons, such as birth defects, hereditary diseases, infection, and trauma.[889] NIDDK-supported research showed that sequencing portions of the genome could help diagnose the underlying cause of severe CKD (requiring a kidney transplant) in children and young adults. Scientists sequenced approximately 400 CKD-linked genes in children and young adults under the age of 25 and identified a genetic cause of CKD in 33 percent of the participants. The likelihood of finding a genetic cause was highest in participants with certain types of CKD, such as conditions known as urinary stone disease and renal cystic ciliopathy.[890] Armed with this genetic knowledge, doctors, patients, and their families could make more informed clinical decisions and tailor treatment strategies to the patients' individual needs.

It is well established that lower blood pressures are associated with substantial cardiovascular and mortality benefit, such as reduced risk for heart disease and stroke. Despite these benefits, a side effect of intensive blood pressure management, compared to less intensive standard management, was thought to be an increased risk of CKD. In contrast to those previous reports, NIDDK-supported scientists have determined that intensive blood pressure control does not lead to kidney injury in people who do not have CKD. Researchers had previously found that, among the subset of study participants who did not have CKD at the start of the trial, those who received an intensive blood pressure control regimen were at a slightly higher risk of developing CKD than those who received standard care. New research, however, showed that a blood flow effect, rather than a bona fide kidney injury, led to the misclassification of CKD in these study participants.[891] Patients and clinicians are now empowered by this new information to seek more intensive blood pressure control to reduce the risk of heart disease, stroke, and other conditions caused by high blood pressure.

Systemic lupus erythematosus (SLE), commonly referred to as lupus, is an autoimmune disease in which the immune system attacks its own tissues. Lupus can affect the joints, skin, lungs, blood cells, brain, heart, and kidneys. Lupus nephritis occurs when lupus autoantibodies affect the kidney structures that filter out waste, and it is the most common severe manifestation of lupus and contributes significantly to mortality in this disease.[892] While current immunosuppressive therapies have been effective in controlling kidney complications and have improved patient survival, they have significant adverse side effects. NIAMS-supported scientists found after studying a mouse model of lupus that pharmacologic blockage of

[885] https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-20-026.html
[886] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-027.html
[887] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-028.html
[888] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-20-029.html
[889] https://www.niddk.nih.gov/health-information/kidney-disease/children
[890] Mann N, et al. *J Am Soc Nephrol* 2019 Feb;30(2):201-215. PMID: 30655312.
[891] Zhang WR, et al. *Ann Intern Med* 2018 Nov 6;169(9):610-618. PMID: 30357395.
[892] https://www.niddk.nih.gov/health-information/kidney-disease/lupus-nephritis

the Hypoxia-inducible factor 1 (HIF-1) protein, which is also being pursued as a novel cancer therapeutic, should be considered as an option in treating patients who have autoimmune tissue damage, including lupus nephritis.[893] Further studies, especially clinical trials in humans, are needed to further explore the benefits of blocking HIF-1 before any treatments become available.

For most people, getting too much sun usually only results in a painful sunburn that lasts a few days to a week, depending on severity. However, in patients with lupus, it has long been known that exposure to sunlight triggers both local skin inflammation and systemic flares, including kidney disease. The cause of this link is poorly understood. NIAMS-funded investigators studying a mouse model showed that a subset of neutrophils (an abundant type of immune cell normally found in the bloodstream) infiltrated ultraviolet (UV) light-exposed mouse skin, dispersed throughout the animals' bloodstream, and traveled to their kidneys. When the researchers blocked the ability of these neutrophils to reach the kidney, UV light-induced kidney inflammation was reduced, indicating that neutrophils mediate the kidney inflammation and damage that occurs following exposure to UV light.[894] While further studies, especially in humans, are warranted to explore the pathogenic role of neutrophils in linking sunlight exposure and systemic inflammation, the current findings raise the possibility of targeting the migration of neutrophils or neutrophils subsets as a novel therapeutic approach for lupus or disease flares.

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited condition that causes small fluid-filled sacs called cysts to develop in the kidneys. Autosomal dominant means that the gene mutation causing the disease only needs to be inherited from one parent. Most people with ADPKD have pain, high blood pressure, and kidney failure at some point in their lives.[895] NIDDK-supported researchers discovered a previously unknown role of exosomes (tiny sac-like cellular structures containing some of the cell's proteins, DNA, and RNA) in the progression of ADPKD in mouse models of the disease. Furthermore, an exosome inhibitor molecule, which blocks exosome release into the blood, delayed kidney cyst growth in mouse models.[896] The results of this study suggest that drug-targeting exosome secretion may be a potential therapeutic strategy to reduce or delay kidney cyst formation in people with ADPKD.

A urinary stone, more commonly called kidney stone, is a solid, pebble-like piece of material that can form in one or both kidneys when high levels of certain minerals are present in the urine. Urinary stones rarely cause permanent damage if treated by a health care professional. The NIDDK-supported Urinary Stone Disease Research Network (USDRN) is conducting research on urinary stones in adults and children in order to learn more about who forms urinary stones, what are the best treatments, and how to prevent stones from forming.[897] One aspect of USDRN is the Prevention of Urinary Stones with Hydration study, which uses financial incentives, coaching, as well as new technology, such as smart water bottles, to

[893] Chen PM, et al. *Sci Transl Med* 2020 Apr 8;12(538):eaay1620. PMID: 32269165.
[894] Skopelja-Gardner S, et al. *Proc Natl Acad Sci U S A* 2021 Jan 19;118(3):e2019097118. PMID: 33397815.
[895] www.niddk.nih.gov/health-information/kidney-disease/polycystic-kidney-disease/autosomal-dominant-pkd
[896] Ding H, et al. *Nat Commun* 2021 Jul 27;12(1):4548. PMID: 34315885.
[897] https://usdrn.org/

encourage participants to drink more water.[898] The study is currently recruiting participants and if successful, doctors and patients will have more tools available to prevent painful urinary stones.

Regenerative Medicine and Improving Kidney Transplant Success

There are many more people in need of kidney transplantations than there are available kidneys for transplanting. Although still a long way off, scientists are making great strides towards being able to grow kidneys and kidney tissues for transplantation in a laboratory. To help advance research in this field, NIDDK supports the Re(Building) a Kidney Consortium to develop revolutionary approaches to restore lost kidney function by creating implantable engineered tissue structures that replicate kidney function, or by directly regenerating tissue in a damaged kidney. The consortium aims to slow or reverse kidney function decline, with the goal of preventing irreversible, debilitating kidney failure.[899] Their research could lead to paradigm-shifting treatment approaches for people with kidney diseases.

For example, NIDDK-supported scientists discovered that streaming fluid across kidney organoids (engineered aggregates of kidney cells) prompts the organoids to develop blood vessels and to form natural tissue structures when grown in the lab. These advancements dramatically improve the extent to which lab-grown organoids replicate normal kidney functions.[900] In the more immediate term, kidney organoids may help researchers test potential new drugs more quickly and accurately than is currently possible. In the longer term, improved kidney organoids represent an important step toward the future development of functional, implantable structures that can enhance or replace lost kidney function in people.

Healthy kidneys filter about a half cup of blood every minute (around 38 gallons per day) removing wastes and extra water to make urine. Their function is highly dependent on the structure and relationship between the blood vessels and kidney tubules that together make up the one million filtering units called nephrons.[901] Thus, blood vessels in the kidney are not uniform, but instead become specialized according to their location to help carry out the precise function of their particular substructure (e.g., retention of sugars and salts, removal of wastes, and reabsorption of water to help maintain fluid balance in the body). NIDDK-supported scientists have identified critical sets of genes turned on in individual cells within discrete, specialized zones of blood vessels in the mouse kidney during development and adulthood.[902] These findings are a window into the molecular pathways that instruct blood, kidney, and other cells on how to come together to form a kidney and could provide a foundation to help accelerate the engineering of functional artificial kidneys.

End-Stage Renal Disease (ESRD) is a medical condition in which a person's kidneys cease functioning on a permanent basis leading to the need for a regular course of long-term dialysis or a kidney transplant to maintain life. African Americans have higher rates of ESRD than European Americans. The *APOL1* genetic variants (differences in the sequence of the *Apolipoprotein L1* gene), which are found primarily among

[898] https://clinicaltrials.gov/ct2/show/NCT03244189
[899] https://www.rebuildingakidney.org/about/
[900] Homan KA, et al. *Nat Methods* 2019 Mar;16(3):255-262. PMID: 30742039.
[901] https://www.niddk.nih.gov/health-information/kidney-disease/kidneys-how-they-work
[902] Barry DM, et al. *Nat Commun* 2019 Dec 13;10(1):5705. PMID: 31836710.

African Americans, are among the only known genetic factors contributing to this health disparity. NIDDK launched the *APOL1* Long-term Kidney Transplantation Outcomes Network to better understand the role of the *APOL1* gene in ESRD risk and disease progression, and to inform future therapies. The long-term goal of this network is to inform clinical practice by providing data on the effects of *APOL1* variants on outcomes of the kidney recipients, providing data regarding the effects of *APOL1* variants on long-term survival and renal functional outcomes of the kidney donors, and establishing a resource of clinical and genetic data, and biological specimens for researchers to use to develop better treatments and therapies to eliminate this health disparity.[903,904]

Risk Factors and Biomarkers for Kidney Diseases

Chronic kidney diseases that cannot be explained by traditional risk factors or known causes continue to be increasingly recognized in specific geographic regions. A notable burden falls on individuals living in poverty, including agricultural workers and other manual laborers. To bring together experts from across the globe to plan strategies for better understanding CKD in these populations to further treatment and therapy development, NIEHS and NIDDK helped sponsor the Third International Workshop on Chronic Kidney Diseases of Uncertain/Non-traditional Etiology in Mesoamerica and Other Regions. Workshop topics covered four broad themes: clinical aspects, burden of disease, mechanisms/causes, and societal response.[905] These meetings are important and influential in bringing together international researchers to focus on solving complex biological questions. A testament to this is the increasing awareness about the seriousness of CKD in these populations; a decade ago in 2012 the disease had yet to be formally recognized, and cross-country and cross-disciplinary collaboration was in its infancy. Despite the recent advances in research, the cause of CKD in these populations remains unclear and better therapies are still needed.

Roughly one in three U.S. adults do not regularly get the recommended amount of uninterrupted sleep that they need to protect their health. Sleep deficiency is linked to many chronic health problems, including heart disease, high blood pressure, diabetes, stroke, obesity, depression, and kidney disease.[906] An NIEHS-research team reported that short sleep and apnea-specific hypoxia, which is the lack of adequate oxygen because of sleep apnea, are associated with CKD in a multi-ethnic population. The findings indicate that sleep disturbance was twice as prevalent among African American participants with CKD compared with White participants. The scientists also found that very short sleep (five or fewer hours per night) and sleep apnea-specific hypoxia were associated with moderate-to-severe CKD.[907] These sleep deficiencies may contribute to CKD by worsening known risk factors, such as dyslipidemia (high cholesterol or fats in blood), hypertension (high blood pressure), and type 2 diabetes. The association between sleep deficiencies and CKD identifies two specific sleep disturbances that could be targeted by clinicians and public health professionals to help prevent or delay the condition and address health disparities.

---

[903] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-024.html
[904] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-025.html
[905] https://www.niehs.nih.gov/health/assets/docs_p_z/report_from_the_workshop_508.pdf
[906] https://www.nhlbi.nih.gov/health/sleep-deprivation
[907] Jackson CL, et al. *Thorax* 2021 Jul;76(7):704-713. PMID: 33277428.

Catching and diagnosing diseases early, before they become severe, is usually associated with better outcomes and overall improved quality of life. Identifying reliable and accurate disease biomarkers—biological molecules found in blood, other body fluids, or tissues that are signs of a condition or disease—is one of the easiest and fastest ways of early diagnosis. NIDDK-supported scientists found that the testican-2 protein could serve as a potential blood-based biomarker for assessing kidney health. Among the scientists' findings was the observation that testican-2 levels directly correlated with standard measures of kidney function. Moreover, in a subset of the study participants, they found that having relatively higher levels of testican-2 at study entry was associated with a lower rate of decline in kidney function and a decreased risk of new-onset chronic kidney disease.[908] These findings lay the foundation for future studies, such as targeted blood tests for testican-2 and direct studies of its association with kidney disease outcomes, that if successful, could mean that doctors would have a new and easy way of assessing kidney function.

Mental Health

Mental illnesses continue to affect millions of Americans, their families, and society. Nearly one in five U.S. adults live with a mental illness (52.9 million in 2020).[909] While there are many different conditions that vary in degree of severity, major depression continues to be one of the most common mental disorders in the U.S., with an estimated 8.4 percent of all U.S. adults reporting a major depressive episode in 2020.[910] Suicide was also among the top ten leading causes of death in the U.S. in 2019.[911] Other chronic mental illnesses reducing the quality of life among Americans include schizophrenia, post-traumatic stress disorder, attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, bipolar disorder, autism spectrum disorder, personality disorders, dissociative disorders, and a range of anxiety and eating disorders. Despite affecting tens of millions of people each year and contributing to lost productivity and reductions in life expectancy, some estimates suggest that only half of those with mental illnesses received treatment in 2020.[912,913] Mental illnesses may also be more prevalent among people who already have other chronic illnesses, such as heart disease, diabetes, cancer, and HIV.[914,915] The multitude of challenges posed by mental illnesses, some of which have become exacerbated during the COVID-19 pandemic, require a variety of innovative efforts supported by several of the 27 ICs across NIH during the past three years of the pandemic to better understand, prevent, and treat these complex and often disabling conditions.

NIMH is the lead federal agency for research on mental illnesses, though several ICOs across NIH focus on aspects of mental illnesses. Activities include the conduct and support of biomedical and behavioral

[908] Ngo D, et al. *Proc Natl Acad Sci U S A* 2020 Oct 6;117(40):25026-25035. PMID: 32958645.
[909] https://www.nimh.nih.gov/health/statistics/mental-illness.shtml
[910] https://www.nimh.nih.gov/health/statistics/major-depression
[911] https://www.cdc.gov/injury/wisqars/LeadingCauses.html
[912] https://www.nimh.nih.gov/health/statistics/mental-illness
[913] 2020 NSDUH Annual National Report. www.samhsa.gov/data/report/2020-nsduh-annual-national-report
[914] Olfson M, et al. *JAMA Psychiatry* 2015;72(12):1172. PMID: 31969473.
[915] Remien RH, et al. *AIDS*. 2019;33(9):1411-1420. PMID: 30950883.

research, health services research, research training, and health information dissemination with respect to the causes, diagnosis, treatment, management, and prevention of mental illnesses.

Understanding Environmental Factors

The interplay between environmental factors and mental illnesses is of interest to NIH and other federal agencies. To increase knowledge about the potential impact of non-social and social environmental factors, several NIH ICs supported longitudinal studies and engaged in interdisciplinary efforts between FY 2019 and FY 2021. Understanding how environmental factors can potentially be beneficial or detrimental will guide NIH's future initiatives to prevent and treat mental illnesses.

Previous research suggests that air pollution may affect mental health.[916,917] Partially supported with funding from NICHD, NIEHS, and NIMH, scientists examined the potential association between air pollution and psychotic experiences by following 2,332 children born in England and Wales in 1994 and 1995.[918] In 2021, the scientists published their study results and concluded that higher levels of air pollution in outdoor settings partly explain the association between urban residence and psychotic experiences in adolescence, which points to the need for global efforts to reduce levels of air pollution and to protect the mental and physical health of young people living in urban areas.

Resources Supporting Collaboration and Innovation

A collaborative effort involving over 200 scientists in 2009 led to the development of the Research Domain Criteria (RDoC) initiative, a research framework for investigating mental disorders through the integration of many levels of information (from genomics to behavior and self-reports) to explore basic dimensions of functioning that span the full range of human behavior.[919] New insights generated by research using the RDoC framework are intended to inform the development of mental health screening tools, revisions to diagnostic systems, and preventive and treatment interventions. In 2019, a new domain, the sensorimotor domain, was recently added to the framework which included the following components: negative valence systems, positive valence systems, cognitive systems, social processes, and arousal and regulatory systems.[920] The new domain consists of four constructs (motor action, agency and ownership, habit, and innate motor patterns), and is intended to encourage a systematic approach to the study of motor function in psychopathology, which will hopefully lead to better treatments for people who are affected with motor system disruptions.[921]

In April 2019, the NIMH Center for Global Mental Health Research (CGMHR) and Grand Challenges Canada co-hosted the 10th Anniversary Conference, Global Mental Health Research Without Borders, which was comprised of plenary sessions, 12 symposiums, five paper panels, 40 poster presentations, networking

---

[916] Ali NA and Khoja A. *Ochsner Journal*. 2019;19(1):4-4. PMID: 30983893.
[917] Gładka A, et al. *International Journal of Occupational Medicine and Environmental Health*. Published online October 3, 2018. PMID: 30281038.
[918] Reuben A, et al. *JAMA Network Open*. 2021;4(4):e217508. PMID: 33909054.
[919] https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc
[920] https://www.nimh.nih.gov/news/science-news/2019/sensorimotor-domain-added-to-the-rdoc-framework
[921] https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/sensorimotor-systems

roundtables, and a training workshop on grant application writing.[922] More than 400 researchers, innovators, and other interested parties from 36 countries attended the two-day conference. In April 2021, the CGMHR and Grand Challenges Canada sponsored the 11th Global Mental Health Research Without Borders Conference, which brought together researchers, innovators, and other interested parties from around the globe to showcase findings from cutting-edge science and explore new opportunities for groundbreaking research.[923] Participants discussed priorities for global mental health for the next decade, with a focus on mental health among youth and the integration of mental health care into health systems and beyond.

To support efforts in expanding early-stage interventions for patients who are at risk of developing schizophrenia, NIMH launched the Accelerating Medicines Partnership® Schizophrenia (AMP SCZ) project as part of the broader AMP program, which aims to identify and validate promising biological targets for therapeutics and is done in collaboration with the Foundation for the National Institutes of Health, the FDA, and multiple public and private partners.[924,925] The overall aims of AMP SCZ are to generate tools to predict individual outcomes and develop targeted interventions for individuals who are at risk for developing schizophrenia. Findings from AMP SCZ studies will enable researchers to develop algorithms that predict the course of illness for individuals at risk for psychosis, allowing for early intervention and testing of treatments that may prevent the development of schizophrenia and improve individuals' clinical and functional outcomes.

NIMH aims to support innovative research ideas and transdisciplinary collaborations that could transform the care of children, adolescents, and adults with severe psychiatric disorders through its Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Research Centers Program. NIMH continues to support the eight mental health research centers that comprise the Research Centers Program, which incorporated a variety of transdisciplinary collaborations and prioritized a deployment-focused approach to yield interventions and service strategies that are relevant and can be rapidly integrated into practice.[926] Many of the centers used digital health platforms and data science methods to learn about mental illness onset and progression in clinical populations, improve diagnosis, and deliver targeted interventions via smart communication technologies. The centers also account for the perspectives of interested parties, including patients, families, and providers, span a variety of key populations and practice settings, and cover a range of scientific and services research.

NIMH convenes workshops that aim to stimulate research on interventions for individuals with mental illnesses and advance understanding of the systems that can contribute to mental disorders. In 2020,

[922] www.nimh.nih.gov/news/events/2019/10th-anniversary-conference-global-mental-health-research-without-borders

[923] https://www.cugmhp.org/events/2021-global-mental-health-research-without-borders-virtual-conference/#:~:text=The%20National%20Institute%20of%20Mental

[924] https://www.nih.gov/research-training/accelerating-medicines-partnership-amp

[925] www.nih.gov/news-events/news-releases/nih-public-private-partnership-advance-early-interventions-schizophrenia

[926] https://www.nimh.nih.gov/research/research-funded-by-nimh/research-initiatives/advanced-laboratories-for-accelerating-the-reach-and-impact-of-treatments-for-youth-and-adults-with-mental-illness-alacrity#:~:text=The%20Advanced%20Laboratories%20for%20Accelerating

NIMH held the NIMH Novel Target Discovery and Psychosocial Intervention Development Workshop which aimed to accelerate research to identify novel drug targets and develop and improve non-pharmacological interventions (such as cognitive, behavioral, and psychosocial approaches) for the treatment of mental illnesses.[927] Workshop participants discussed their rationales for selecting the mechanistic affective/cognitive/social processes they chose to target with their interventions, as well as the utility of cross-disciplinary efforts to support the successful translation of basic findings to clinical application. In 2020, NIMH also hosted a virtual workshop that sought to stimulate discussions among experts and identify experimental approaches and emerging technologies for analyzing the genetic contribution to neurodevelopmental and psychiatric disorders.[928] Summaries of NIMH event proceedings are available on the NIMH website.[929]

During the COVID-19 pandemic, NIMH convened virtual workshops focused on services and practices. In 2020, NIMH hosted the virtual workshop, Transforming the Practice of Mental Health Care*,* which included discussions around advances in technology, such as AI/ML, to accelerate the practical use of data to inform personalized mental health care.[930] In 2021, NIMH conducted a webinar, during which presenters provided an overview of an NIMH-funded study that adapted an evidence-based mental health intervention for LGBTQ+ youth of color and their families.[931] Summaries of these NIMH events are archived and available on the NIMH website.

Emotional well-being and its core components—a sense of balance in emotion, thoughts, social relationships, and pursuits—is a key component of NIH's broader objective of fostering health promotion and disease prevention. In 2021, new NIH funding totaling $3.13 million was awarded to support the creation of five new research networks and allow investigators to refine and test key concepts that advance the study of emotional well-being.[932] The new research networks will aim to advance the field by facilitating transdisciplinary research in the social, behavioral, psychological, biological, and neurobiological sciences and encourage information dissemination and collaboration among leading scientists through meetings, conferences, small-scale pilot research, and multidisciplinary cross training.

Emerging data shows an association of neurologic and psychiatric symptoms being observed with COVID-19.[933,934,935] In July 2021, NIMH, NINDS, and NIA co-hosted the Neurologic and Psychiatric Effects of SARS-

[927] https://www.nimh.nih.gov/news/events/announcements/nimh-novel-target-discovery-and-psychosocial-intervention-development-workshop
[928] https://www.nimh.nih.gov/news/events/2020/virtual-workshop-genes-to-biology-integrative-systematic-approaches-for-revealing-biological-functions-of-psychiatric-risk-genes-and-alleles
[929] https://www.nimh.nih.gov/news/events/2020
[930] www.nimh.nih.gov/news/events/2020/virtual-workshop-transforming-the-practice-of-mental-health-care.
[931] https://www.nimh.nih.gov/news/events/2021/advancing-evidence-based-interventions-to-improve-access-to-mental-health-services-for-lgbtq-youth
[932] https://www.nih.gov/news-events/news-releases/nih-networks-advance-emotional-well-being-research
[933] Roy D, et al. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. Published online August 5, 2020:1-16. PMID: 32753076.
[934] Heneka MT, et al. *Alzheimer's Research & Therapy*. 2020;12(1). PMID: 32498691.
[935] Edinoff AN, et al. *Psychiatry International*. 2022;3(2):158-168. doi:10.3390/psychiatryint3020013

CoV-2 Meeting.[936] The virtual meeting included research presentations on the gaps and priorities regarding neurologic and psychiatric complications associated with symptoms of long COVID, or what physicians refer to as post-acute sequelae of SARS-CoV-2. The meeting also served as a forum to examine data related to neurologic and psychiatric complications of COVID-19 infection and possible interactions with other central nervous system infections. The information shared will be used to guide further research into this area.

Suicide Prevention

Suicide is a major public health concern. NIH continues to support research on risk factors, prevention interventions, and care models. NIH also developed informative brochures and resources on suicide prevention that are publicly available.

Suicide is one of the leading causes of death in the U.S., with nearly 46,000 people dying by suicide in 2020.[937] NIMH supports research aimed at identifying individuals and populations (including racial and ethnic minority populations, sexual and gender minorities, and youth) most at risk for suicide, understanding the causes of suicide risk, developing suicide prevention interventions, and testing the effectiveness of these interventions and services in real-world settings. NIMH-funded researchers have developed evidence-based suicide prevention tools that can be implemented in the health care system, such as the Ask Suicide-Screening Questions tool that takes about 20 seconds to administer. In 2021, NIMH-funded researchers developed the computerized adaptive screen for suicidal youth which can help emergency departments quickly identify individuals in need of connection to suicide prevention services.[938,939,940] In addition, NIMH supports research to determine feasible and effective approaches to limit access to lethal means, such as firearms.

Despite advances in the treatment of depression and other serious mental illnesses, there remain few evidence-based interventions that rapidly reduce suicide risk within health care settings.[941] Research shows that up to 80 percent of people who die by suicide visit health care settings in the year before their death, and about one-fifth of people who die by suicide are seen in a health care setting within the week of their death.[942] In 2021, NIMH supported new research projects that focus on testing the safety, efficacy, and feasibility of several of the newest antidepressant interventions. These interventions include ketamine and intranasal esketamine, which are known to rapidly reduce depressive symptoms in hours or days, as well as transcranial magnetic stimulation (a noninvasive treatment which uses magnets to activate specific parts of the brain) to rapidly reduce suicidal thoughts and behaviors in adults and

[936] https://www.nimh.nih.gov/news/events/2021/neurologic-and-psychiatric-effects-of-sars-cov-2-meeting
[937] https://www.cdc.gov/suicide/index.html
[938] www.nimh.nih.gov/news/science-news/2021/adaptive-screener-may-help-identify-youth-at-risk-of-suicide
[939] King CA, et al. *JAMA Psychiatry*. 2021;78(5):540. PMID: 33533908.
[940] https://www.nimh.nih.gov/research/research-conducted-at-nimh/asq-toolkit-materials
[941] Dillon CB, et al. *Journal of Affective Disorders*. 2020;276:898-906. PMID: 32739708.
[942] Ahmedani BK, et al. *Journal of General Internal Medicine*. 2014;29(6):870-877. PMID: 24567199.

adolescents.[943,944] Identifying and developing rapid-acting treatments may help accelerate recovery and could reduce the likelihood of repeated hospitalizations and self-harming thoughts and behaviors.

NIMH hosted several meetings to highlight findings and identify challenges and opportunities in suicide prevention research. In 2020, NIMH held the two-day virtual workshops, which brought together clinician scientists, behavioral scientists, neuroscientists, geriatric psychiatrists, epidemiologists, and implementation scientists.[945] Workshop participants discussed the urgent need to advance mechanistic understanding of the link between social disconnection and suicide risk, identify treatment targets for promising interventions to address social disconnection and suicide in late-life, and eliminate barriers to providing services to socially disconnected older adults. In June 2021, NIMH also hosted the four-part virtual research roundtable series, which brought together a diverse group of expert panelists to assess the state of the science and short and longer-term research priorities related to preteen suicide risk and risk trajectories.[946,947]

Autism Spectrum Disorder

CDC estimates that about one in 44 eight-year-old children have been diagnosed with ASD in 2018.[948] Between FY 2019 and FY 2021, NIH supported research to improve ASD treatment outcomes and develop better screening and detection of ASD. NIH also participates in the Interagency Autism Coordinating Committee, a federal advisory committee that is designed to coordinate Federal efforts and provide advice to the HHS Secretary on issues related to ASD. The committee is composed of representatives from various U.S. Department of Health and Human Services agencies, the Department of Education, Labor, Justice, Veteran Affairs, and Housing and Urban Development, and other governmental organizations, as well as public members, including individuals with ASD and representatives of patient advocacy organizations.

NIMH supports research to improve interventions and outcomes for individuals on the autism spectrum. In 2020, NIMH renewed the award for the Autism Biomarkers Consortium for Clinical Trials (ABC-CT), a multisite study seeking to develop biomarkers which could be used to separate individuals with ASD into distinct subgroups for clinical trials, and ultimately lead to more predictive and personalized treatment.[949,950] ABC-CT researchers began evaluating a set of promising eye-tracking markers and developed an electroencephalogram (EEG) biomarker that measures neural activity associated with face

---

[943] Xiong J, et al. *Journal of Psychiatric Research*. 2021;134:57-68. PMID: 33360864.
[944] Hallett M. *Neuron*. 2007;55(2):187-199. PMID: 17640522.
[945] https://www.nimh.nih.gov/news/events/2020/virtual-workshop-social-disconnection-and-late-life-suicide-mechanisms-treatment-targets-and-interventions
[946] https://www.nimh.nih.gov/news/events/2021/understanding-suicide-risk-among-children-and-pre-teens-a-synthesis-workshop
[947] https://www.robertfrostpta.org/index.php/announcements/risk-resilience-trajectories-in-preteen-suicide-synthesis-workshop-free-webinar-from-nimh
[948] https://www.cdc.gov/ncbddd/autism/addm.html
[949] https://www.nimh.nih.gov/news/research-highlights/2020/testing-and-refining-biomarkers-to-support-intervention-research-for-children-with-autism
[950] Webb SJ, et al. *Frontiers in Integrative Neuroscience*. 2020;13. PMID: 32116579.

processing.[951] The EEG biomarker was accepted by the FDA's Center for Drug Evaluation and Research Biomarker Qualification Program as a potential stratification marker in future ASD clinical trials.

Developing and validating early screening and detection methods for ASD risk is vital for providing early intervention services and optimizing developmental outcomes. In 2021, researchers funded by NIMH and NICHD developed a mobile application that was successful at distinguishing toddlers later diagnosed with ASD from typically developing toddlers based on the toddlers' eye movements while watching videos that included social cues.[952,953] In 2020, to further support the goal of identifying autism in the first year of life, NIMH partnered with NICHD, NINDS, and NIDCD to award over $4 million to seven research projects aimed at developing and validating screening tools for early detection. The funded projects seek to translate findings related to early signs of autism into practical ASD screening tools that can be implemented across various settings with the goal of providing interventions as soon as possible, so that outcomes for each child can be maximized.

Mental Health Disparities Research

Minority populations are often disproportionately affected by poor mental health outcomes. Between FY 2019 and FY 2021, several NIH ICOs supported research to advance policies and practices to address the needs of communities that are underserved and underrepresented in mental health research, promote equity in access to care and treatment, and reduce disparities in treatment outcomes. In addition to funding research and training opportunities, NIH has developed toolkits, downloadable publications, and other resources that are publicly available.

Individuals from racial, ethnic, sexual, and gender minority groups, socioeconomically disadvantaged populations, and underserved rural populations experience striking mental health disparities in the burden of illness, access to care, and engagement in care and recovery. In 2020, NIMH issued two requests for information on innovative research strategies and priorities to improve mental health outcomes and reduce or eliminate mental health disparities in affected populations.[954,955] Relatedly, in response to the alarming rise in suicide rates in Black youth and a call to action from Congress in 2019, NIMH funded a number of studies aimed at optimizing suicide risk detection and interventions among Black youth.[956] In 2021, NIMH continued to partner with NIMHD to support three collaborative research hubs which aim to develop and increase the reach of effective, culturally relevant preventive interventions to reduce the burden of suicide and promote resilience among American Indian and Alaska Native youth. The ongoing collaboration led to the development of a protective factor framework for suicide prevention that adopts a social ecological perspective and community-level intervention paradigm.[957] In 2021, NIMH, together

[951] McPartland JC, et al. *Frontiers in Integrative Neuroscience*. 2020;14. PMID: 32346363.
[952] https://www.nimh.nih.gov/news/science-news/2021/media-advisory-prototype-app-for-mobile-devices-could-screen-children-at-risk-for-autism-spectrum-disorder
[953] Chang Z, et al. *JAMA pediatrics*. 2021;175(8):827-836. PMID: 33900383.
[954] https://grants.nih.gov/grants/guide/notice-files/NOT-MH-20-073.html
[955] https://grants.nih.gov/grants/guide/notice-files/NOT-MH-21-190.html
[956] A Report to Congress from The Congressional Black Caucus Emergency Task Force on Black Youth Suicide and Mental Health. *Ring the Alarm: The Crisis of Black Youth Suicide in America*. 2019. https://www.stevefund.org/wp-content/uploads/2019/12/FULL-TASKFORCE-REPORT.pdf
[957] Allen J, et al. *Prevention Science*. Published online June 24, 2021. PMID: 34169406.

with NIMHD and NICHD, convened a virtual conference entitled Identifying Opportunities and Priorities in Youth Mental Health Disparities Research.[958]

Several collaborative efforts are underway across NIH to address striking differences in the prevalence, course, and severity of mental illnesses, access to quality health care, and health outcomes based on sex, gender, age, race, ethnicity, and geography. In November 2020, NIMH and NIMHD conducted a virtual workshop that brought together a diverse group of researchers to identify innovative approaches to understanding and addressing disparities across major areas of mental health science and research.[959] Workshop panels spotlighted the impact of discrimination, stigma, and social media on mental health disparities, preventive and treatment interventions and access to and engagement in health services, implementation research, and innovation in analytics and methods. NIMH, NIMHD, and the larger research community are now able to use the information from the workshop to better understand how to support and further expand research on reducing mental health disparities.

Information Dissemination and Community Engagement

NIH supports the development of networks and resources to support the public and research communities. Several events, workshops, and tools were developed to disseminate information, foster engagement, and support collaborative efforts among interested parties.

NIMH offers authoritative information about mental disorders and findings from the latest mental health research.[960] NIMH updated several health-topic pages, fact sheets, and brochures on the NIMH website to provide the latest information to interested parties, including individuals living with mental illnesses, their families, mental health service providers, and voluntary community organizations. The website now features expanded access to its Spanish content with a new Spanish landing page and translations of key health topic pages, brochures, fact sheets, and social media resources. NIMH also created new products of interest for the community and expanded social media resources through a new Digital Shareables section of the website to provide shareable resources such as graphics, GIFs, and infographics that community members can use to raise awareness about mental health.[961] Members of the public can now subscribe to the new *Discover NIMH* e-newsletter to learn about these tools and resources for community education.

Brain Awareness Week is a global campaign to foster public enthusiasm and support for brain science.[962] Each year, NIMH staff and scientists participate in the National Museum of Health and Medicine's Brain Awareness Week program by sharing interactive and fun activities to help kids learn about the brain and the impact neuroscience research has on our everyday lives. As part of the program, NIMH highlights facts and resources about the brain on its social media channels. NIMH also created a new series of coloring

[958] https://www.nimh.nih.gov/news/events/2021/2021-youth-mental-health-disparities-conference-identifying-opportunities-and-priorities-in-youth-mental-health-disparities-research
[959] https://www.nimh.nih.gov/news/events/2020/workshop-identifying-new-directions-in-mental-health-disparities-research-innovations-with-a-multidimensional-lens
[960] https://www.nimh.nih.gov/health
[961] https://www.nimh.nih.gov/get-involved/digital-shareables
[962] https://medicalmuseum.health.mil/?p=education.brain_awareness_week.index#:~:text=Week%20at%20NMHM

and activity books to educate kids about the brain and stress, a new science education webpage to highlight NIMH's STEM activities, and numerous new graphics and GIFs for use on social media.[963]

NIMH engages with external interested parties through two NIMH-coordinated groups: the Alliance for Research Progress and the Professional Coalition for Research Progress. The Alliance for Research Progress is a group of patient and family advocates from national voluntary organizations representing individuals with mental illnesses as well as their family members and caretakers. The Professional Coalition for Research Progress is a group of senior leaders and representatives from national professional organizations with an interest in NIMH research. In October 2020, NIMH brought the Alliance and Coalition together in a town hall that featured presentations from NIH staff about ongoing mental health research initiatives, a discussion panel with presenters, and a question-and-answer session with Dr. Joshua Gordon, Director of NIMH, outlining NIMH's new outreach approach to increase public access to mental health research, and to facilitate communication between NIMH, professional societies, and advocacy groups.[964]

NIMH uses social media to share the latest research findings, funding and training opportunities, and information and resources on mental illnesses. Between FY 2019 and FY 2021, NIH hosted many social media events in recognition of national observances such as Eating Disorders Awareness Week, World Bipolar Day, Post-Traumatic Stress Disorder Awareness Month, ADHD Awareness Month, and Borderline Personality Disorder Awareness Month. In response to the COVID-19 pandemic, NIMH hosted social media events on suicide prevention, re-entry stress for children and adolescents, and managing stress and anxiety.[965,966,967] To respond to questions from academic entrepreneurs and small businesses about funding and application processes, NIMH hosted Reddit Ask Me Anything events.[968,969]

U.S. adolescents from minority groups are more vulnerable to mental health problems than other adolescents and are also less likely to use mental health services.[970,971] In 2019, NIMH invited students ages 16 to 18 years old to participate in the Speaking Up About Mental Health! essay contest.[972] The contest aimed to address disparities in mental health treatment and services and spur further

[963] https://www.nimh.nih.gov/get-involved/science-education
[964] https://www.nimh.nih.gov/news/events/2020/townhall
[965] https://www.nimh.nih.gov/news/events/2021/livestream-event-on-suicide-prevention-during-covid-a-continuing-priority
[966] https://www.nimh.nih.gov/news/events/2021/instagram-event-back-to-school-coping-with-the-pandemic-and-re-entry-stress
[967] https://www.nimh.nih.gov/news/events/2021/livestream-event-managing-stress-and-anxiety
[968] https://www.nimh.nih.gov/news/events/2020/reddit-ask-me-anything-with-dr-margaret-grabb-nimhs-small-business-research-programs
[969] www.nimh.nih.gov/news/events/2019/nimh-reddit-ask-me-anything-with-dr-jane-pearson-suicide-prevention
[970] Office of the Surgeon General (US); Center for Mental Health Services (US); National Institute of Mental Health (US). *Mental Health: Culture, Race, and Ethnicity: A Supplement to Mental Health: A Report of the Surgeon General*. PMID: 20669516.
[971] Alegria M, et al. *Child and Adolescent Psychiatric Clinics of North America*. 2010;19(4):759-774. PMID: 21056345.
[972] https://www.nimh.nih.gov/news/science-news/2019/nationwide-essay-contest-challenges-high-schoolers-to-be-frank-about-mental-health

conversations about mental health among high schoolers. In their essays, writers discussed ways to address the stigma and social barriers that adolescents from minority populations may face when seeking mental health treatment. This contest was started as part of the Healthy Mind Initiative, which is led by NIMHD and aims to increase mental health awareness and promote suicide prevention in Asian American and Pacific Islander youth.[973]

Monitoring and Planning Activities

In 2020, NIMH released its new Strategic Plan for Research which builds on the successes of previous NIMH strategic plans and provides a framework for advancing research priorities that support the Institute's mission and addresses new challenges in mental health.[974] NIMH developed the strategic plan with input from a variety of interested parties, including NIMH leadership and staff, the National Advisory Mental Health Council, federal and private partners, as well as feedback from organizations, advocacy groups, and people with lived experiences via a request for information (RFI) seeking public comment. NIMH also devoted a section of its website to the Strategic Plan for Research.[975] The NIMH Strategic Plan is updated annually to keep pace with ever-evolving scientific approaches and research priorities. Findings from NIMH-funded investigators are also posted on progress pages for each of the plan's four goals.

In 2020, the NIMH Director called for the formation of a Drug Development Workgroup of the National Advisory Mental Health Council (NAMHC) to assess the state of clinical trial research within the Institute to ensure that current strategies support effective early-stage drug development efforts. The workgroup divided into five subgroups (Target Engagement, Fast-Fail and Rapid Testing of Mechanisms, Vulnerable Clinical Trial Populations, Confirmatory Efficacy Trials, and Workforce) and summarized their recommendations in the 2020 NAMHC Workgroup Report on Drug Development.[976] The report recommendations consistently emphasized the need to continue building a clinical trials program that focuses on the quantitative assessment of drug pharmacology as it relates to brain function. In addition, the workgroup recommended that NIMH continue to train investigators from across multiple disciplines and support them with clinical trial resources.

Advances to Improve Prevention and Treatment

Approximately one in eight women in the U.S. report symptoms of postpartum depression.[977] In 2019, the FDA approved brexanolone as the first drug specifically designed to treat postpartum depression.[978] Research conducted in the 1980s in NIMH's Intramural Research Program contributed to the formulation

[973] https://nimhd.nih.gov/programs/edu-training/hmi/
[974] https://www.nimh.nih.gov/news/science-news/2020/new-nimh-strategic-plan-paves-the-way-for-advances-in-mental-health-research
[975] https://www.nimh.nih.gov/health/publications/strategic-plan-for-research
[976] https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/2020-namhc-workgroup-on-drug-development
[977] https://www.cdc.gov/reproductivehealth/vital-signs/identifying-maternal-depression/index.html
[978] www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-post-partum-depression

of this new therapy.[979] FDA approval represents the final phase of a bench-to-bedside journey for this drug.

Chronic stress and exhaustion can put many caregivers at risk for various physical and psychological morbidities. Given the increasing demand for caregivers, and with close to 20 percent of informal, unpaid caregivers across the U.S. reporting fair or poor health,[980] the need for interventions that promote caregiver health and well-being is increasingly acknowledged. In 2019, NINR-funded researchers reported the findings of a randomized controlled trial among dementia caregivers to test the effects of Life Enhancing Activities for Family Caregivers (LEAF),[981] a six-week positive emotion regulation intervention on outcomes of positive emotion, depression, anxiety, and physical health as measured by the Patient-Reported Outcomes Measurement Information System® (PROMIS®). The online LEAF intervention promotes capitalizing on positive events, gratitude, mindfulness, positive reappraisal, personal strengths, attainable goal setting, and acts of kindness. The study found that the intervention was effective at increasing positive emotion.[982] The study also found that the intervention improved caregiving skills, decreased levels of depressive symptoms and anxiety, and improved physical health as defined by PROMIS® self-report measures. The results of the randomized controlled trial suggest that the LEAF intervention may help to improve the well-being of dementia caregivers who experience high levels of stress and depression.

Generalized anxiety disorder (GAD) is a condition characterized by excessive anxiety and worry. Cognitive behavioral therapy (CBT) is an effective first-line, evidence-based psychotherapy for GAD, but many who might benefit do not receive CBT because of cost, stigma, or logistical reasons. Increasingly, people are seeking alternative interventions, such as yoga, outside the medical system. In 2021, NCCIH-funded researchers reported the findings of a randomized clinical trial to assess whether Kundalini yoga and CBT for GAD are each more effective than a control condition (stress education) and whether yoga equates to the effects of CBT for the treatment of GAD.[983] The trial included 230 adults who had a primary diagnosis of GAD. The interventions were Kundalini yoga, CBT, and a control stress education intervention that involved lectures on the effects of stress and lifestyle behaviors and the importance of exercise and diet. The difference between the CBT and stress education groups was significant, but the difference between the Kundalini yoga and stress education groups was not. An additional analysis did not find Kundalini yoga to be as effective as CBT at 12 weeks or the six-month follow-up. The researchers concluded that Kundalini yoga may be a helpful, but only moderately potent, intervention for GAD. The results of the study suggest that focusing future research on individual characteristics that make a person more likely to respond to

[979] https://www.nimh.nih.gov/about/director/messages/2019/a-bench-to-bedside-story-the-development-of-a-treatment-for-postpartum-depression
[980] Edwards VJ, et al. Characteristics and Health Status of Informal Unpaid Caregivers — 44 States, District of Columbia, and Puerto Rico, 2015–2017. MMWR Morb Mortal Wkly Rep 2020;69:183–188. DOI: http://dx.doi.org/10.15585/mmwr.mm6907a2external icon
[981] https://leafstudy.ucsf.edu/leaf-life-enhancing-activities-family-caregivers
[982] Moskowitz JT, et al. *Health Psychology*. 2019;38(5):391-402. PMID: 31045422.
[983] Simon NM, et al. *JAMA Psychiatry*. Published online August 12, 2020. PMID: 32805013.

yoga versus CBT could help inform how yoga might be integrated into a personalized approach to anxiety disorders.

People with psychosis experience cognitive impairments and some loss of contact with reality, which can disrupt school, work, and social relations. NIMH-funded research, including results from the Recovery After an Initial Schizophrenia Episode Study, found that early treatment of psychosis symptoms increases the chance of successful recovery.[984] Building on this foundation, NIMH supported a broad research initiative known as the Early Psychosis Intervention Network (EPINET) which aims to enhance coordinated specialty care delivery to people with symptoms of early psychosis, promote research to improve diagnosis, interventions, and outcomes in early serious mental illness, and increase access to resources for researchers, providers, and families.[985] In 2021, EPINET expanded its network of research hubs and launched the EPINET web portal. Individuals and families can now find multiple resources related to early psychosis on the new portal, including an interactive map of EPINET clinics around the U.S.[986]

Other Research Advances to Understand Risk Factors and Underlying Biology

Eating disorders, including anorexia nervosa, bulimia nervosa, and binge-eating disorder are serious mental illnesses that can lead to severe complications and death. NIMH-funded researchers advanced knowledge about eating disorder behaviors, such as binge-eating, purging, and restricting food intake, by showing that these behaviors alter brain reward response processes and food intake control circuitry.[987] The researchers concluded that changes to internal reward responses could maintain, reinforce, or worsen eating disorder behaviors, emphasizing how eating disorder behaviors and neurobiology interact to reinforce vicious cycles and make recovery difficult. Researchers are currently investigating potential treatments that would target and change eating disorder behaviors to achieve lasting recovery.

Researchers found that patients with osteoarthritis or acute joint injury had high levels of the G protein-coupled receptor kinase 2 (GRK2) protein in their cells. GRK2 drives cell growth, but following joint injury, such growth becomes pathologic and further exacerbates damage to the surrounding tissue. Researchers found that patients with osteoarthritis had high levels of GRK2 in their cartilage cells. [988] In one of their experiments however, the researchers found that the GRK2 inhibitor Paroxetine—an FDA-approved antidepressant commonly used to treat depression, panic attacks, and anxiety—could return cartilage cells back to a normal state and preserve the cartilage surface. Mice treated with paroxetine did not have pathologic cartilage cell growth, indicating that paroxetine may facilitate regeneration and could be useful to prevent or treat osteoarthritis.[989]

---

[984] https://www.nimh.nih.gov/health/topics/schizophrenia/raise

[985] https://www.nimh.nih.gov/news/research-highlights/2021/nih-initiative-expands-access-to-resources-for-early-psychosis-treatment-and-research

[986] https://nationalepinet.org/

[987] Frank GKW, et al. *JAMA Psychiatry*. Published online June 30, 2021. PMID: 34190963.

[988] Karuppagounder V, et al. *Osteoarthritis and Cartilage*. 2020;28:S92. doi:10.1016/j.joca.2020.02.141.

[989] Carlson EL, et al. *Science Translational Medicine*. 2021;13(580):eaau8491. PMID: 33568523.

Anti-depressant use, especially long-term use, has increased in the U.S. and there is growing evidence suggesting that anti-depressant use may lead to increased risk of bone fracture in certain populations.[990] In 2020, NIAMS- and NIA-funded researchers published results of an evaluation of varying anti-depressant classes on bone outcomes and determined that cortical bone (hip, non-vertebrae) decreases in older women taking certain anti-depressants, particularly selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors.[991] Data from this study offers a possible mechanism for anti-depressants in bone health and demonstrates actions that may increase fracture risk, particularly at sites such as the hip and wrist in older women.

Musculoskeletal and Skin Diseases

Many different types of musculoskeletal and skin diseases, those of the bones, joints, muscles, and skin, affect millions of Americans. For example, 18.8 percent of women over age 50 have osteoporosis in the neck or spine.[992] Psoriasis, a chronic autoimmune skin disease, affects more than 7.4 million American adults.[993] Musculoskeletal and skin diseases often occur as complications from other conditions, compounding the impact on a person's quality of life and health. NIH, with NIAMS as the lead IC in this research area, investigates the basic mechanisms behind these diseases and conditions, explores how and why they develop, and searches for new ways to treat and prevent them.

Advancing Muscle Biology Research to Inform Better Diagnostics, Drugs, and Therapies

Muscular dystrophies are a group of muscle diseases caused by mutations in a person's genes. Over time, muscle weakness decreases mobility, making everyday tasks difficult. There are many kinds of muscular dystrophy, each affecting specific muscle groups, with signs and symptoms appearing at different ages, and varying in severity.[994] Muscles repair themselves by stimulating muscle stem cells to divide and become mature muscle cell. To identify genes involved in muscle repair, researchers used single cell RNA-sequencing technologies to sequence the gene transcripts of thousands of individual muscle stem cells taken from normal and damaged muscles to identify patterns. Importantly, the thousands of stem cells from damaged muscles were likely to contains a diverse range of cells, from those just starting to become muscle cells, to those half-way between stem cells and muscle cells, to those just finishing becoming muscle cells. With the help of computer analyses, the researchers took advantage of these different stages of muscle repair to identify the distinct gene signatures present within each stage.[995] In the future, a better understanding of these development and repair processes could inform the development of genetic therapies to treat muscular dystrophies.

Duchenne muscular dystrophy (DMD) is a rare genetic disease that causes muscle weakness, difficulty walking, and early death, and it affects boys almost exclusively. About 1 in 5,000 boys are born with DMD.[996] The disease has no cure, so it ultimately leads to severe disability and death. Even with intensive

[990] Rizzoli R, et al. *Bone*. 2012;51(3):606-613. PMID: 22659406.
[991] Agarwal S, et al. *Bone*. 2020;140:115552. PMID: 32730935.
[992] https://www.cdc.gov/nchs/fastats/osteoporosis.htm
[993] https://www.cdc.gov/psoriasis/
[994] https://www.cdc.gov/ncbddd/musculardystrophy/facts.html
[995] Dell'Orso S, et al. *Development* 2019 Apr 11;146(12):dev174177. PMID: 30890574.
[996] https://www.cdc.gov/ncbddd/musculardystrophy/facts.html

study, only two new drugs for treating DMD have been approved in the last 15 years. This is partly because the disease is rare, so it is often difficult to recruit enough patients to conduct a high-quality clinical trial. Another reason is that the tests most commonly used to determine if a drug works in muscular dystrophy, such as tests of walking ability, cannot be used in younger children who are not yet walking well. These tests are often inconsistent and unreliable in older children. Researchers have long hoped to find a simple blood test that can indicate whether a drug is working in patients with DMD, but no such blood marker has yet been found. In a recent study, a team of NICHD-supported scientists used technology similar to that used in newborn screening to identify a collection of proteins which, when measured in combination, accurately identified differences between patients with and without DMD—even before DMD patients began to show symptoms.[997] This technology may therefore help researchers conduct clinical trials in younger DMD patients, who may experience the greatest potential benefit from future interventions.

Open muscle biopsy—making a small incision through the skin into the muscle and removing a small piece of muscle tissue—is an integral part of most clinical studies on DMD and all dystrophies. However, the patient population is particularly vulnerable to the injury caused by the biopsy, and repeated open muscle biopsies of the same muscle are not recommended. To determine if a less invasive type of biopsy called core needle muscle biopsy—using a large needle to take out a piece of muscle tissue—could effectively replace open muscle biopsy, NIAMS-supported investigators performed a retrospective analysis of nearly 500 needle biopsies at one DMD clinical trial. They found that the procedure retrieved high quality tissue with minimal complications. While the volume of muscle tissue was lower than an open muscle biopsy, the resulting injury was reduced with core needle biopsy and repeated measure of the same limb was possible six months later, which is not recommended with open muscle biopsy.[998] These findings should allow researchers to better collect clinical trial data necessary to advance new therapies.

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common forms of muscular dystrophy. The disease can progress slowly and in a somewhat unpredictable pattern, making clinical trial design to test investigational therapies particularly challenging. At any one time, some muscles in an FSHD patient can appear almost normal, while others show active disease, presenting a diagnostic challenge. NIAMS supported researchers performed an MRI scan on the lower limbs of 36 people with FSHD, followed by needle biopsies of accessible muscles in the same limbs. They found that a strong signal with a specific type of MRI was approximately 90 percent predictive of muscles that showed active disease.[999] In the future, these findings might allow doctors to better identify which muscles to focus targeted treatments.

In addition to muscle wasting, DMD patients often develop osteoporosis, where the bones become weak and brittle so that even a minor fall can cause a fracture. NIAMS-funded researchers sought to better understand whether muscle weakening and osteoporosis were related. Using a severe DMD mouse model, the investigators showed that a combination of abnormal activation of two proteins, RhoA and ROCK, and infiltration of immune cells call macrophages into muscle tissues increases the formation of

[997] Alayi TD, et al. *ACS Omega* 2020 Oct 6;5(41):26504-26517. PMID: 33110978.
[998] Barthelemy F, et al. *Muscle Nerve* 2020 Dec;62(6):688-698. PMID: 32820569.
[999] Wang LH, et al. *Hum Mol Genet* 2019 Feb 1;28(3):476-486. PMID: 30312408.

calcium deposits in muscles. Blocking the abnormal activation of RhoA and ROCK prevented calcium from being deposited in muscle cells.[1000] Their results, if confirmed in human patients, could provide an avenue to restore calcium balance between human patient muscle and bone and improve DMD symptoms.

DMD is caused by defects (changes to the DNA sequence) in a specific gene that results in a truncated protein called dystrophin. If scientists could determine how to leverage gene editing technologies to correct the error in the DNA of muscle cells, they could potentially treat, or alleviate some symptoms, of DMD. Using the CRISPR gene editing technology, which can precisely cut out and insert small pieces of DNA to repair a defective gene, NICHD-supported scientists tested a variety of corrective edits in mice with errors similar to those found in humans. They also edited cells from DMD patients. In both the mice and human cells, the edits restored a more complete version of dystrophin. The researchers also found that the amount of gene-editing agent they used influenced the number of corrected cells.[1001] This research is an important step that may translate into new ways to treat DMD.

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure, while exercise is defined as planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness.[1002] Loss of muscle mass is a devastating consequence of aging and disease, and not everyone can counter this loss through exercise, necessitating the need for other means of preventing muscle loss. NIAMS-funded researchers screened over 10,000 unique molecular events in muscles following resistance exercise and found that 2,000 of them were potentially involved in exercise-stimulated muscle growth. However, a small group of 38 molecular events were not affected by a chemical known to inhibit protein synthesis, and one of those was activation of the TRIM28 protein. Increasing the production of TRIM28 to high levels in muscle led to an increase in muscle fiber size, but when TRIM28 was inhibited in muscle fibers, fiber size decreased, and the muscles had a blunted response to muscle-building stimuli.[1003] Understanding the molecular events that lead to muscle mass gains through experiments such as this may lead to therapeutic targets, like TRIM28, that mimic exercise or amplify the effect of exercise.

For over 100 years, the force generating machinery inside muscle cells was considered to be made up of many individual, parallel contractile units (imagine a handful of uncooked spaghetti noodles) all working together. Using state of the art, three-dimensional imaging approaches, researchers discovered that the muscle contractile machinery is quite different from this model. Instead, it is made up of a frequently branching, highly connected mesh-like network united across the entire muscle cell. While all mammalian muscle cells (including human) contain highly connected contractile networks, the number of connections and branch points changes during muscle maturation and differs among mature muscle types (e.g., heart, fast-twitch, slow-twitch).[1004] Since many human pathologies, such as muscular dystrophies, autoimmune

[1000] Mu X, et al. *Aging (Albany NY)* 2020 Dec 23;12(24):24853-24871. PMID: 33361519.
[1001] Min YL, et al. *Sci Adv* 2019 Mar 6;5(3):eaav4324. PMID: 30854433.
[1002] Caspersen CJ, et al. Public Health Rep. 1985 Mar-Apr;100(2):126-31. PMID: 3920711.
[1003] Steinert ND, et al. *Cell Rep* 2021 Mar 2;34(9):108796. PMID: 33657380.
[1004] Willingham TB, et al. *Nat Commun* 2020 Jul 24;11(1):3722. PMID: 32709902.

and neurological diseases, and aging are associated with alterations in muscle fiber organization, these findings will open up new avenues of research that could lead to novel therapies.

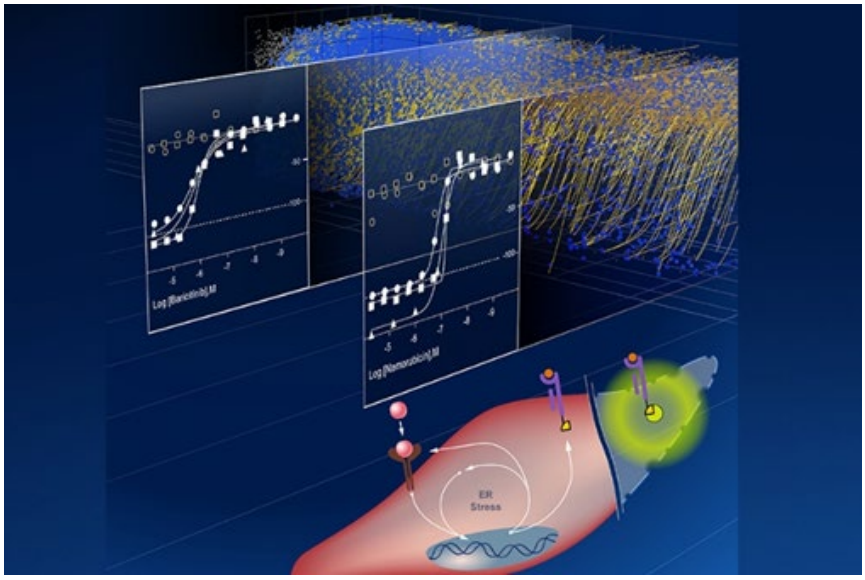


Figure 24: NCATS Team's Rapid Test Finds Promising Therapies for Myositis. Credit: NCATS and NHGRI; created by Darryl Leja (NHGRI)

Idiopathic inflammatory myopathy, also known as myositis, is a rare muscle disease with no effective therapies and few experimental treatments in development. Myositis is an autoimmune disease characterized by chronic inflammation of the muscles, leading to skeletal muscle weakness and pain, as well as complications in the skin, lungs, and circulatory system. NCATS scientists rapidly tested 4,679 unique compounds at different concentrations, using NCATS' library of thousands of existing investigational and FDA-approved drugs to assess their pharmacological effects on a key inflammatory pathway believed to be involved in myositis. Of the thousands of drugs tested, NCATS scientists identified 12 drugs and compounds that showed the most promise.[1005,1006] The next step is to test these 12 drugs in animal models of myositis to identify which are candidates for human trial.

Malignant hyperthermia is a potentially fatal disorder that can cause people to have a severe reaction to certain drugs used for anesthesia, such as a dangerously high body temperature, rigid muscles or spasms, a rapid heart rate, and other symptoms. Without treatment, it can be fatal. A new mouse model, with a gene mutation similar to that found in humans with increased risk for malignant hyperthermia, displayed differences in mitochondrial function and evidence of increased oxidative stress, known to cause disruptions in cellular signaling.[1007] These differences seen in the mutant mice could explain why people with malignant hyperthermia react severely to anesthesia and, in some cases, present with skeletal muscle disorders. Therefore, the basic mechanisms found in this mouse research could lead to

[1005] https://ncats.nih.gov/news/releases/2020/ncats-teams-rapid-test-finds-promising-therapies-for-myositis
[1006] Kinder TB, et al. *ACS Chem Biol* 2020 Jul 17;15(7):1974-1986. PMID: 32459468.
[1007] Chang L, et al. *J Biol Chem* 2020 Nov 6;295(45):15226-15235. PMID: 32826313.

determining the underlying issues in the broader patient population and inform the development of new therapies.

Chronic musculoskeletal pain conditions are common in the adult population and studies suggest they may also be frequent among children and youth. An NCCIH supported study found that young people receiving care for chronic musculoskeletal pain in the U.S. are prescribed medicine more often than nondrug treatments, such as physical therapy or health education. The study also found that opioid prescriptions in the 18- to 24-year age group are close to the level previously reported in adults with musculoskeletal pain.[1008] Surprisingly, little evidence exists on the effectiveness of medications for treating chronic musculoskeletal pain in children and adolescents. These finding suggest that better ways to increase health care providers' use of evidence-based nonpharmacologic approaches are needed.

The Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs) are designed to foster the translation of new scientific findings and technological developments into novel treatments for muscular dystrophies. The Centers promote basic, translational, and clinical research and provide important resources that can be used by the national muscle biology and neuromuscular research communities. The Centers also engage patients and patient advocates in educational programs. Centers include one or more scientific research resource cores that support the specific projects and serve as a resource for the international research community.[1009,1010] In 2019, NIH conducted an evaluation of the centers, identifying best practices for achieving the Wellstone Centers' goals of supporting impactful research on the muscular dystrophies, developing and distributing resources to accelerate research, facilitating the training of the next generation of researchers, and enabling connections within the patient community.[1011] For more information on the Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, please see the Chapter 4 of this report.

Advancing Bone and Cartilage Biology Research to Inform Better Diagnostics, Drugs, and Therapies

Osteoporosis is a condition that causes the bones to become weak and brittle so that even a minor fall can cause a fracture. In FY 2019, NIAMS, NIA, and ODP hosted a Pathways to Prevention Workshop on the appropriate use of drug therapies for osteoporotic fracture prevention to identify research gaps and suggest focus areas that could move the field forward.[1012] Following the workshop, an independent panel issued a report[1013] that lays the foundation for future research activities that took into consideration an Agency for Healthcare Research and Quality (AHRQ) systematic review of the scientific evidence,[1014] speaker presentations, audience input, and public comments. Federal agencies are currently developing strategies for disseminating and implementing these findings, including soliciting research proposals on

[1008] Feldman DE and Nahin RL. *J Pediatr* 2021 Jun;233:212-219.e1. PMID: 33524388.
[1009] https://www.wellstonemdcenters.nih.gov/
[1010] https://www.nichd.nih.gov/research/supported/mdsrc
[1011] Wellstone Center Evaluation Working Group. *Evaluation of the Paul D. Wellstone Muscular Dystrophy Research Centers*. 2019. https://wellstonemdcenters.nih.gov/sites/wellstone/files/WellstoneCenterEvalRptExecSumm-508.pdf
[1012] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/appropriate-use-drug-therapies-osteoporotic-fracture-prevention
[1013] Siu A, et al. *Ann Intern Med* 2019 Jul 2;171(1):51-57. PMID: 31009943.
[1014] https://effectivehealthcare.ahrq.gov/products/osteoporosis-fracture-prevention/research

promoting research on mechanisms of pathogenesis and pathophysiology of atypical femoral fracture and osteonecrosis of the jaw[1015] and leveraging existing large databases and cohorts to better understand the risks and benefits of long-term osteoporosis therapy and interrupted therapy (e.g., drug holidays).[1016]

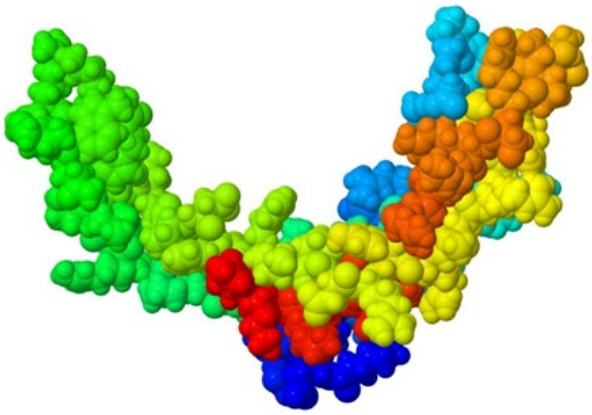


Figure 25: NIAMS-funded Research Sets the Stage for New Osteoporosis Therapy. Credit: RCSB Protein Data Bank.[1017]

More than ten million people in the U.S. have osteoporosis, which is most common in women who have gone through menopause. In April 2019, the FDA approved the drug romosozumab for the prevention of osteoporotic fractures in postmenopausal women. The drug blocks the effects of the protein sclerostin and works mainly by increasing new bone formation.[1018] The development of this therapy is based on a body of NIAMS-funded work that helped to establish the therapeutic targets, specifically, proteins in the Wnt signaling pathway, for the treatment of osteoporosis and other skeletal diseases. These studies included several rare bone diseases that predispose patients to dramatic changes in bone mass, such as osteoporosis pseudoglioma, sclerosteosis, and Van Buchem disease. Subsequent studies of two proteins in the Wnt pathway, lipoprotein receptor-related proteins 5 and 6 (LRP5/6) and sclerostin, have provided important insights into the mechanisms of how these proteins regulate skeletal homeostasis. Pharmaceutical companies are currently testing a drug to block sclerostin in other bone diseases such as osteogenesis imperfecta.

While broken bones frequently rejoin and heal after a simple cast to hold them in place or a surgery to realign them, sometimes they are broken severely enough that bone cannot regrow and reconnect on its own. The current gold standard repair for these critical-sized defects is autologous bone grafting, a technique where bone taken from a different part of the patient's body is implanted at the site of the missing bone. However, this procedure is associated with complications including infection and pain, in addition to the limitation of the availability of the autologous bone. Both fat and bone are derived from

[1015] https://grants.nih.gov/grants/guide/notice-files/NOT-AR-21-006.html
[1016] https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-22-018.html
[1017] www.rcsb.org/3d-view/jsmol/2kd3
[1018] https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-osteoporosis-postmenopausal-women-high-risk-fracture

the same type of stem cell called an adipose-derived stem cell. Fat tissues are abundantly available and more easily harvested than bone. Thus, NIAMS-supported researchers investigated an alternate approach of removing fat stem cells, genetically modifying them to overexpress the bone morphogenetic protein 2 (BMP-2) bone growth factor and then reimplanting them into bone wounds. They successfully demonstrated that fat stem cells overexpressing BMP-2 can heal critical-sized defects in the large leg bone of rats.[1019] Future success of this research in larger animals could lead to less cumbersome and more promising treatment options for complicated fractures in humans without the complications associated with transplanting autologous bone material.

Cartilage is a firm, flexible, whitish connective tissue found in the external ear, tip of the nose, joints that separate moving bones (e.g., knee, elbow, fingers), and a few other areas within the body. Cartilage can become damaged from injury (e.g., sports injury), or from gradual wear and tear (osteoarthritis), leading to pain, swelling, and restricted moments. NIAMS supported researchers are exploring the use of mesenchymal stem cells (MSCs)—precursor cartilage cells—to repair cartilage defects. This procedure requires MSCs to develop into mature cartilage cells, called chondrocytes, that will effectively mimic and integrate into the native tissue. Successfully stimulating MSCs to become mature chondrocytes in culture requires the optimization of dozens of compounds to mimic the natural environment of the body. Researchers first provided MSCs a molecular scaffold to grow on, which is much closer to the natural environment than the standard flat, plastic cell culture plate. They also cultured the MSCs together with a mature cartilage cell called an articular chondrocyte because the molecular signals released by them can stimulate the development of MSCs into chondrocytes.[1020] This and future studies will advance cartilage repair techniques and could lead to the development of biomaterials and therapeutic strategies to treat cartilage defects more successfully.

Cartilage injuries do not often heal by themselves and are a common source of joint pain. They can also lead to osteoarthritis, the wearing down of cartilage between movable bones, making the joint pain worse and more frequent. Large gaps in cartilage can be repaired by transplanting healthy cartilage grafts into the gap, but these grafts fail to integrate well into the surrounding tissues, creating a microscopic gap between the graft and native cartilage. NIAMS-funded researchers described the development of a synthetic, biodegradable fiber mesh to promote better integration of cartilage grafts with host cartilage. This mesh incorporates a growth factor, called insulin-like growth factor 1 (IGF-1), to attract cartilage cells called chondrocytes to the gap between graft and host cartilage, which in turn promotes production of healthy cartilage in the gap region.[1021]

Surgery to permanently connect two or more vertebrae in the spine to prevent movement between them, known as spinal fusion, is one of the most common types of orthopedic surgeries. Current approaches that incorporate bone growth factors to speed recovery are associated with complications such as swelling, fluid buildup, and the formation of bone in undesired locations. NIAMS-funded researchers recently improved a 3D-printed scaffold to facilitate bone regeneration and blood vessel growth by

[1019] Vakhshori V, et al. *Bone* 2020 Sep;138:115524. PMID: 32622870.
[1020] Kim YS, et al. *J Control Release* 2020 Dec 10;328:710-721. PMID: 33010336.
[1021] Boushell MK, et al. *Ann N Y Acad Sci* 2019 Apr;1442(1):138-152. PMID: 30985969.

optimizing the scaffold's pore size and geometry without the need for additional growth factors. Results in a rat model of spinal fusion were favorable,[1022] suggesting that this material holds great promise as a clinically translatable biomaterial for use as a bone graft substitute in orthopaedic procedures requiring bone regeneration.

Each of the spinal vertebrae are separated by a shock-absorbing structure, called an intervertebral disc, to prevent the bones from rubbing and grinding against each other during movement, especially physical exertions like running and jumping. Intervertebral disc disease is the breakdown or degeneration of one or more intervertebral discs and is one of the major causes of low back pain. Intervertebral discs are composed of a soft, gelatinous central portion called the nucleus pulposus (NP) surrounded by a hard outer ring called the annulus fibrosus (AF). NIAMS-supported researchers found that the initial stages of disc herniation (when the inner NP pushes through a crack in the outer AF) are asymptomatic because the NP is largely protected from damage by inflammation by the hard outer AF. Once the damage becomes severe enough for the inner NP cushion to be accessible by inflammatory molecules and cells, symptom onset begins.[1023] These findings may lead to earlier detection of herniated discs, which should give doctors and patients time to take corrective actions before symptoms worsen.

Each year, 300,000 Americans over the age of 64 are hospitalized for hip fractures.[1024] Disability as a result of hip fracture is a serious problem as it is a difficult fracture to recover from, and afterward many people are not able to live on their own. A recent NIAMS-funded study provides the first controlled clinical data on two types of surgical options that will aid in clinical decision-making to manage disability post hip fracture. Among people who could walk independently before experiencing a hip fracture, total hip replacement (called hip arthroplasty) was only associated with modestly better function over 24 months compared to hemiarthroplasty (replacing half the hip), but it had a slightly higher incidence of serious adverse events.[1025] The findings that total hip arthroplasty has limited advantages as well as the possible higher risk of complications are important not only for the aging U.S. population, but may be particularly important in regions of the world where total hip arthroplasty is not easily accessible or is cost prohibitive.

Knee osteoarthritis (OA), more commonly known as wear-and-tear arthritis, is caused by the degradation of cartilage within the knee. There are currently no effective drugs for treating the causes of knee OA, so many patients are prescribed pain medications to reduce the discomfort. Current guidelines for knee OA management recommend non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line pharmacologic treatment for patients with symptoms such as pain. Using the Osteoarthritis Initiative longitudinal cohort, NIAMS-supported researchers found that NSAIDs may actually accelerate the progression of knee OA.[1026] Clinical trials are required to further confirm these results and inform future treatment guidelines.

Lower-extremity joint symptoms such as knee pain and stiffness are leading causes of disability in older adults. Physical activity prevents disability and improves health outcomes, but there is no clinical evidence

[1022] Hallman M, et al. *Tissue Eng Part A* 2021 Jan;27(1-2):26-36. PMID: 32098585.
[1023] Gorth DJ, et al. *J Bone Miner Res* 2020 Apr;35(4):725-737. PMID: 31800975.
[1024] https://www.cdc.gov/falls/hip-fractures.html
[1025] HEALTH Investigators, Bhandari M, et al. *N Engl J Med* 2019 Dec 5;381(23):2199-2208. PMID: 31557429.
[1026] Perry TA, et al. *Rheumatology (Oxford)* 2021 Oct 2;60(10):4624-4632. PMID: 33502488.

to establish the minimum amount of time and intensity of physical activity needed. Using data from more than 1,500 Osteoarthritis Initiative participants aged 50 years or older, NIAMS-funded investigators found that one hour of moderate-to-vigorous physical activity per week, which is less than ten minutes a day, can significantly reduce the risk of mobility disability for patients with symptoms of knee osteoarthritis.[1027] This minimum threshold and the associated wide range of health benefits of exercise may motivate inactive older adults to begin their path toward a physically active lifestyle.

Advancing Skin Biology Research to Inform Better Drugs and Therapies

Severe burns can be life-threatening, often requiring surgery to remove the damaged skin as well as the surgical removal of healthy skin from an uninjured site on the patient and transplantation of the skin graft to the burn injury. Although removing healthy skin from one area and transplanting it to another area (called an autograft) is effective, it can lead to complications such as increased pain, infection, and scarring. In June 2021 the FDA approved a treatment for adults with thermal burns that have some remaining deep skin layers but require surgery to repair. The product is a combination of two types of skin cells and a collagen matrix. It resembles the rectangular sheet of skin a surgeon would remove from a donor site for such treatment, making it easy for surgeons to integrate it into their practices.[1028,1029] Small Business Innovation Research (SBIR) support from NIAMS and NIGMS were instrumental in supporting the early technology and research needed for the company, Stratatech, to develop this product.

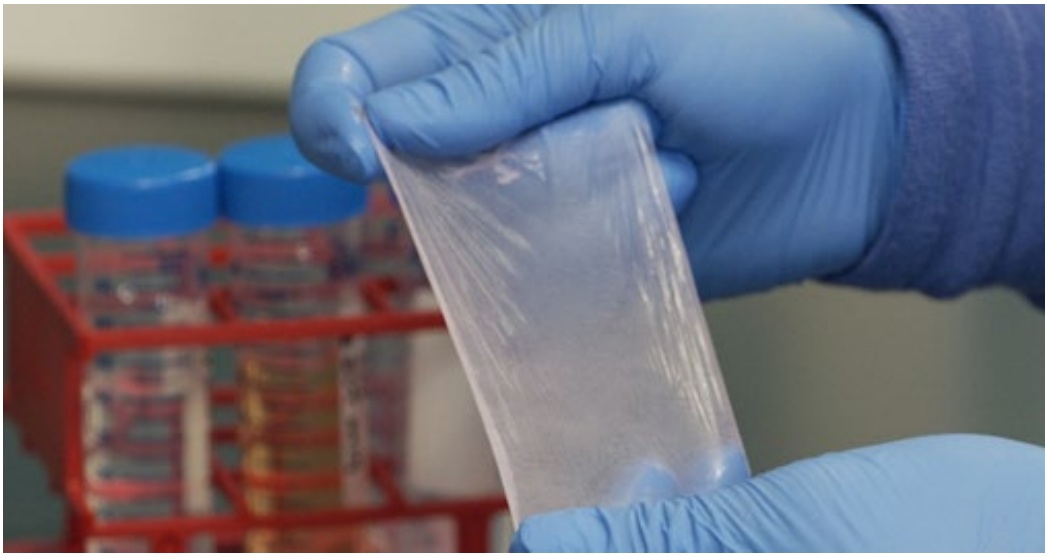


Figure 26: New Skin Substitute Provides Alternative to Skin Graft for Thermal Burns. Credit: Courtesy of Stratatech Corp

A large benefit of biomedical research is that the findings are rarely limited to one specific area, but rather provide insights and clues to many different diseases or areas of the body. For example, NIAMS-supported researchers focused on skin inflammation and diseases yielded important discoveries in diseases affecting other tissues such as bone and joints. The investigators discovered that overexpression of the kallikrein-

[1027] Dunlop DD, et al. *Am J Prev Med* 2019 May;56(5):664-672. PMID: 30902564.
[1028] https://seed.nih.gov/portfolio/stories/stratatech
[1029] www.fda.gov/news-events/press-announcements/fda-approves-stratagraft-treatment-adults-thermal-burns

related peptidase 6 (KLK6) protein in the skin promotes psoriasis-like inflammation (rash with itchy, scaly patches) in a mouse model. Interestingly, the psoriasis-like skin inflammation observed in animals also leads to progressive axial skeletal bony changes and peripheral joint inflammation that resembles inflammation seen in psoriatic arthritis (PsA), a type of severe and disabling joint inflammation that develops in some psoriasis patients. This suggests that the KLK6 protein and its downstream signaling pathway may be a novel therapeutic avenue to explore for patients with PsA,[1030] which is especially important since no treatments currently used to treat PsA patients is effective at reducing joint inflammation.

Figure 27: Hairy Human Skin Generated from Stem Cells. Credit: Koehler lab, Nature

Skin is the body's largest organ and plays a vital role in health. It helps regulate body temperature, retain body fluid, and defend against the outside world. It also allows the sensation of touch and pain. Scientists have been able to grow human skin outside the body for over 40 years. However, skin grown in cultures lacked embedded structures found in real skin, such as hair follicles and sweat glands. Recently, NIAMS, NICHD, and NIDCD-supported investigators developed a skin model in the laboratory that improves on previously engineered skin equivalents in that it develops both the upper and lower skin layers and contains many specialized structures found in skin, including hair, fat, and nerves.[1031,1032] Being able to create skin in the lab that more closely resembles real skin may help advance research into skin development and diseases, and could have implications for treating burn patients and baldness.

Wounds in the mouth heal faster and without scar formation compared with skin wounds. Understanding the differences between the healing processes in the mouth and skin could help researchers develop better treatments that heal skin wounds much faster and with less scarring. Scientists previously found that the superior oral wound healing is facilitated by the SRY-Box Transcription Factor 2 (SOX2) protein, which regulates the expression of hundreds of genes that code for proteins that are responsible for rapid wound healing. NIAMS-funded scientists used a mouse model to begin identifying those downstream

[1030] Billi AC, et al. *J Clin Invest* 2020 Jun 1;130(6):3151-3157. PMID: 32155135.
[1031] https://www.nih.gov/news-events/nih-research-matters/hairy-human-skin-generated-stem-cells
[1032] Lee J, et al. *Nature* 2020 Jun;582(7812):399-404. PMID: 32494013.

genes and proteins.[1033] Their findings have broad implications on the biology of wound healing and define potential clinical targets for therapeutic development to treat skin wounds.

Skin wounds, with rare exception, heal with fibrotic scars that severely disrupt tissue architecture and function. NIAMS-funded researchers discovered that a drug called imiquimod, which is currently used to treat precancerous skin lesions caused by excessive sun exposure, can help mouse ear wounds heal without scarring. The scientists found that imiquimod acts on the transient receptor potential cation channel, subfamily A, member 1 (TRPA1) protein, which is a pain sensor found in cells within the nervous system. Upon activation by imiquimod, TRPA1 can mobilize immune cells, which are well known for their ability to fight germs, to promote scarless healing.[1034] Because of this advance, it is expected that imiquimod and similar drugs acting on TRPA1 will be tested soon in humans.

Obesity

Four out of every ten U.S. adults (41.9 percent) are affected by obesity,[1035] and around 19.7 percent (roughly 14.7 million) of children and adolescents have obesity,[1036] making it one of the most common and complicated chronic diseases afflicting Americans. Childhood obesity puts children at increased risk for future health problems, and obesity-related problems among adults include dangerous health issues, such as heart disease, stroke, type 2 diabetes, and some forms of cancer. Furthermore, obesity is estimated to cost the U.S. nearly $173 billion in annual medical spending.[1037] 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.

Prevention and Risk Factors

Early childhood education, usually covering preschool through kindergarten, is thought to provide a wide variety of benefits that last well into adulthood, including more likely to have higher-paid jobs and less likely to be involved in unlawful behavior. NICHD-funded researchers are adding 'less likely to be obese in adulthood' to this growing list. Children in high-poverty neighborhoods who participated in a comprehensive preschool program that provided parents with health and educational services, job training, and gave kids healthy meals and taught them how to make healthy food choices, had a lower BMI in their late 30s than a similar group who participated in the usual early childhood programs.[1038,1039]

Sleeping with a television or light on in the room may be a risk factor for gaining weight or developing obesity. Although an unhealthy high-calorie diet and sedentary behaviors are the most common risk factors for weight gain, they are not the only risk factors. Exposure to artificial light at night while sleeping

[1033] Uchiyama A, et al. *J Invest Dermatol* 2019 Aug;139(8):1809-1820.e8. PMID: 30772301.
[1034] Wei JJ, et al. *Sci Immunol* 2020 Aug 28;5(50):eaba5683. PMID: 32859683.
[1035] https://www.cdc.gov/obesity/data/adult.html
[1036] https://www.cdc.gov/obesity/data/childhood.html
[1037] Ward ZJ, et al. PLoS ONE 2021 Mar 24;16(3): e0247307. PMID: 33760880.
[1038] https://www.nichd.nih.gov/newsroom/news/032221-preschool-BMI
[1039] Reynolds AJ, et al. *JAMA Pediatr* 2021 Jun 1;175(6):637-640. PMID: 33749715.

is associated with increased weight gain and development of obesity in women, according to NIEHS researchers. Not all light is equal; using a small nightlight was not associated with weight gain, whereas women sleeping with a light or television on were 17 percent more likely to have gained weight (approximately 11 pounds) during the follow-up period. The study only included women and was the first to describe this association in humans.[1040,1041]

NIEHS and NIDDK researchers uncovered how a high-fat diet rewires the brain and encourages fatty food consumption over nutritionally balanced diets. The findings partly explain the difficulty of dieting. The researchers fed one group of mice a standard diet and another group a high-fat diet. When the mice receiving the high-fat diet were switched to a standard diet, they refused to eat. Research from other groups found that a dense cluster of neurons located in the brain's hypothalamus, called agouti-related peptide producing neurons, are responsible for the unpleasant sensations associated with hunger and the motivating drive to eat. The presence of food turns these neurons off along with the unpleasant sensations that they trigger. In the mice switched from high-fat diet to standard diet, these neurons were no longer functioning correctly; they did not turn off in the presence of food as expected but continued to signal a desire to eat high-fat food.[1042,1043]

The COVID-19 pandemic has had widespread negative health effects that go beyond the typical symptoms of infections, including adverse effects on mental health, sleep, diet and exercise, and alcohol consumption. NICHD-funded researchers have identified changes in screen time and physical activity that may increase kids' obesity risk. Compared to before the pandemic, children 7- to 12-years old increased their sedentary behavior, screen time, and food intake, while reducing their level of physical activity and adopting a later sleep schedule. These are all behaviors that increase obesity risk, and they exceed changes traditionally seen during summer breaks.[1044,1045] While troubling, these trends are comparing 2018 and 2019 (pre-pandemic) with 2020, the first year of the pandemic when the most severe restrictions were implemented. Further research is needed to determine whether these obesity-promoting behaviors continue to persist.

Obesity is a major risk factor for cardiometabolic diseases, however, a substantial proportion of individuals with obesity do not develop cardiometabolic diseases. A new analysis of human genetic data sets by NIDDK-funded scientists has revealed regions of the genome that are linked to both elevated levels of body fat and protection from some of the negative health impacts of obesity. Some of these body fat-increasing genes are associated with storage of excess fat beneath the skin as opposed to storage around the internal organs where fat is metabolically harmful. Other genes were found to be functionally implicated in improved blood glucose levels, insulin signaling, regulation and development of fat cells, and energy (calorie) expenditure.[1046] These results are helping to clarify the complex genetic underpinnings of

[1040] Park YM, et al. *JAMA Intern Med* 2019 Aug 1;179(8):1061-1071. PMID: 31180469.
[1041] https://factor.niehs.nih.gov/2019/7/feature/2-feature-light/index.htm
[1042] Mazzone CM, et al. *Nat Neurosci* 2020 Oct;23(10):1253-1266. PMID: 32747789.
[1043] https://factor.niehs.nih.gov/2020/10/papers/dir/index.htm#a4
[1044] Burkart S, et al. *Pediatr Obes* 2022 Jan;17(1):e12846. PMID: 34409754.
[1045] https://www.nichd.nih.gov/newsroom/news/083121-COVID-19-impact
[1046] Huang LO, et al. *Nat Metab* 2021 Feb;3(2):228-243. PMID: 33619380.

obesity, and the genes identified may represent targets for new therapies to reduce cardiometabolic risk associated with excess body fat.

Our circadian rhythms (24-hour sleep-wake cycle) and metabolic processes (food consumption and digestion) are regulated together, and when disrupted can lead to weight gain and metabolic health issues. New research supported by NIDDK has clarified how the microbes in the gut (the gut microbiome) regulate the mice's daily metabolic rhythms that are associated with sleeping and feeding cycles. The scientists discovered that the microbiome affects the activity of the histone deacetylase 3 intestinal protein, which is involved in cyclic gene activity in the gut. They also found that this protein controls how intestinal cells absorb nutrients during digestion, ultimately affecting the concentrations of metabolic products and lipids in the mice's blood. When scientists put the mice on a high-fat diet, this protein in the intestinal lining was required for the microbiome to promote obesity and other negative metabolic effects.[1047] The findings highlight a possible way in which the gut microbiome's regulation of its host's metabolism has significant impacts on metabolic health and point toward potential new targets for the treatment of metabolic disease if similar microbiome effects are found in humans.

NIDDK researchers found that a diet of mainly ultra-processed foods (those with ingredients predominantly found in industrial food manufacturing) causes overeating and weight gain. For the study, they recruited 20 men and women to live at the NIH Clinical Center for four weeks and eat a diet of ultra-processed foods and a diet of unprocessed foods for two weeks each. The ultra-processed and unprocessed meals presented to the participants had the same amounts of calories, sugar, fat, salt, and fiber, and the participants could eat as much or as little of each meal as they wanted. On the ultra-processed diet, the study participants consumed 500 more calories per day and gained about two pounds on average, while the same individuals lost about two pounds during their time on the unprocessed diet.[1048,1049] Although further studies are needed to understand what aspects of the ultra-processed foods caused overeating and weight gain, limiting consumption of ultra-processed foods could be an effective strategy for losing weight and obesity prevention.

Treatments and Clinical Guidelines for Obese Patients

Total knee replacement (TKR) is generally accepted as the definitive treatment for advanced knee osteoarthritis (OA) after patients fail nonoperative treatments. Although TKR provides the greatest improvement in quality of life in patients with advanced knee OA, many surgeons remain hesitant to operate on patients with morbid obesity (body mass index greater than 39.9 kg/m^2) because of increased risks for more short-term complications postoperatively. However, there is a lack of scientific evidence to support these suspicions. NIAMS-funded investigators used an innovative, validated computer simulation called the Osteoarthritis Policy Model to demonstrate that TKR is a cost-effective treatment for patients aged 50 years and older who have both advanced knee OA and extreme obesity, including those with

[1047] Kuang Z, et al. *Science* 2019 Sep 27;365(6460):1428-1434. PMID: 31604271.
[1048] Hall KD, et al. *Cell Metab* 2019 Jul 2;30(1):67-77.e3. PMID: 31105044.
[1049] https://www.cc.nih.gov/sites/nihinternet/files/internet-files/about/news/newsletter/2019/summer/CCNewsSummer2019.pdf

obesity related conditions such as cardiovascular disease or type 2 diabetes.[1050] These findings have important clinical care and policy implications for patients with knee OA.

People affected by obesity are more likely to develop osteoarthritis and tend to develop it earlier than people that are not affected by obesity. However, it is unclear whether joint damage accumulates primarily as a result of physical strain from excess body weight or as a result of other biological processes such as metabolism and inflammation that are exacerbated by being overweight. To address this question, researchers studied the joints of genetically modified mice with a defect in fat storage. The mice are largely unable to produce fat tissue, and store excess fat in other areas of the body, such as the liver, muscles, joints, and other tissues. Surprisingly, while the genetically modified mice became overweight, their joints were no worse off than those of normal mice, and they accrued less joint damage in response to trauma. This study suggests that fat tissue signaling contributes to osteoarthritis in people with obesity and likely outweighs the role of mechanical factors in the context of obesity-induced osteoarthritis.[1051]

Over one-third of youth are considered overweight or to have obesity, with minority and low-income youth at greatest risk for obesity and related diseases. Increasing physical activity levels has been shown to positively impact youth weight status, cardiorespiratory fitness, metabolic health, and body composition. A recent study, co-funded by NINR and NICHD, tested a physical activity intervention through a randomized controlled trial among low-income middle school students in afterschool programs. The intervention added Get-to-Know-You sessions and physical activity sessions designed to address the social developmental needs of early adolescents (e.g., fostering friendships, group belonging, and social skills) to existing afterschool programs. An analysis of the program showed almost one hour of additional weekly moderate-to-vigorous physical activity in those in the intervention arm of the study.[1052] The results provide support for physical activity interventions to incorporate social factors in programs for underserved youth and can inform future school-based health initiatives.

Bariatric surgery involves making physical changes to the digestive system (e.g., removing most of the stomach) to facilitate weight loss in people with severe obesity.[1053] It is always voluntary and done as a last resort when the obesity is severe, causing serious health problems, and diet and exercise have not worked. NIDDK supports the Teen Longitudinal Assessment of Bariatric Surgery observational study[1054] to assess the short- and long-term risks and benefits of bariatric surgery among teens with severe obesity and serious weight-related health problems, who were already planning to have the surgery. One analysis utilized data from two independent studies evaluating outcomes in teens who had bariatric surgery compared to adults who had obesity since adolescence and went on to have surgery in adulthood. The researchers found that five years after weight-loss surgery, both groups achieved similar weight loss, but adolescents had remission of diabetes and hypertension more often than adults.[1055] This study

[1050] Chen AT, et al. *Ann Intern Med* 2021 Jun;174(6):747-757. PMID: 33750190.
[1051] Collins KH, et al. *Proc Natl Acad Sci U S A* 2021 Jan 5;118(1):e2021096118. PMID: 33443201.
[1052] Zarrett N, et al. *J Behav Med* 2021 Jun;44(3):379-391. PMID: 33677766.
[1053] https://www.niddk.nih.gov/health-information/weight-management/bariatric-surgery
[1054] www.niddk.nih.gov/about-niddk/research-areas/obesity/bariatric-surgery-teens-severe-obesity-study-teen-labs
[1055] Inge TH, et al. *N Engl J Med* 2019 May 30;380(22):2136-2145. PMID: 31116917.

demonstrates that bariatric surgery at a younger age may provide significant health benefits, potentially avoiding adverse effects of prolonged severe obesity into adulthood. In another study, researchers found that adults with severe obesity who underwent bariatric surgery had significantly more short- and long-term (five years later) weight loss compared to people with severe obesity who did not have bariatric surgery.[1056] These findings reinforce previous studies showing bariatric surgery could be safe and effective at causing prolonged weight loss.

Maintaining a diet and exercise regime to lose weight is very difficult. Unfortunately, it is even more difficult to maintain the new, lower weight and not regain the lost weight over time—of all the challenges facing researchers and patients in treating obesity, regain of lost weight is likely the most difficult challenge of all. The bold NIDDK-supported Physiology of the Weight-reduced State consortium launched in 2021 following a 2019 workshop will characterize the physiological mechanisms underlying individual variability in maintenance of reduced weight over time. The investigators will study adults with obesity before and after weight loss from a behavioral/lifestyle intervention to understand appetite and metabolic adaptations to reduced weight.[1057,1058] This research may lead to novel strategies for maintaining weight loss.

Excess gestational weight gain occurs in two-thirds of pregnancies and can lead to metabolic impairments in the mother and increased risk for obesity in the child. NIDDK-funded researchers have provided, for the first time, evidence-based recommendations for energy intake (caloric intake) in pregnant women with obesity. Their findings suggest that pregnant women with obesity should not consume extra calories during the second and third trimesters and that the energy needs of the fetus are met by mobilizing maternal fat stores to achieve healthy delivery of the infant. Importantly, these findings challenge the current recommendations for women with obesity.[1059] This is a pioneering study in its field that can potentially help improve obstetrical care. Future research could lead to the implementation of new, evidence-based recommendations for calorie intake in pregnant women with obesity.

Exercise provides a large array of beneficial effects, from reduced stress and improved mental wellbeing, to improved cardiovascular health and reduced risks for diabetes and other metabolic diseases. Scientists are just beginning to understand the molecular pathways that underlie these benefits. Through a highly comprehensive analysis, researchers have revealed molecular changes involved in a choreography of biological processes, including metabolism, inflammation, cardiovascular function, and tissue repair, that occur in humans in response to an acute bout or single session of exercise. Exercise triggered the release of several hormones, as analyzed through blood samples, to restore metabolic balance, and the team also observed a decrease in the appetite-associated hormones leptin and ghrelin, suggesting a role of physical activity in appetite regulation.[1060] The results provide a window into why exercise is good for us and offer the potential to someday be implemented into health care settings as a personalized blood test for fitness to determine an optimal fitness regimen. In two other studies, researchers identified molecules that

[1056] Arterburn DE, et al. *Ann Surg* 2021 Dec 1;274(6):e1269-e1276. PMID: 32187033.
[1057] https://www.niddk.nih.gov/news/meetings-workshops/2019/physiology-of-weight
[1058] Laughlin MR, et al. *Obesity (Silver Spring)* 2021 Apr;29 Suppl 1(Suppl 1):S5-S8. PMID: 33759392.
[1059] Most J, et al. *J Clin Invest* 2019 Aug 1;129(11):4682-4690. PMID: 31369400.
[1060] Contrepois K, et al. *Cell* 2020 May 28;181(5):1112-1130.e16. PMID: 32470399.

regulate muscle adaptations and metabolic conditioning in mice and humans in response to exercise.[1061,1062] These studies and future ones like them may lead to the identification of molecular pathways that can be targeted by drugs to provide a similar beneficial effect as exercise.

Gaining new insights into the link between diabetes and higher risk of dementia, NIDDK-supported scientists discovered, through research in mice, that insulin and the related hormone insulin-like growth factor 1 (IGF-1) act in multiple parts of the brain to regulate blood glucose (sugar) levels, memory, and other vital mind and body processes. To identify areas of the brain important for insulin and IGF-1 control of metabolism and cognitive functions, the researchers generated two groups of mice with reduced signaling by these hormones in specific regions of the brain, the hippocampus and central amygdala, respectively, and examined the effects. The results from this research in mice illuminate critical roles of the hormones insulin and IGF 1 in multiple areas of the brain and yield new insights into the connections between insulin action, metabolism, learning and memory, and anxiety-like behavior.[1063,1064] These findings may lead to new ideas for therapies in humans, not only for diabetes and obesity, but also for AD and other dementias.

Pulmonary Diseases

Many different types of pulmonary diseases affect the lungs and respiratory system. Chronic obstructive pulmonary disease (COPD), for example, has been diagnosed in more than 16 million Americans.[1065] Another common pulmonary disorder is sleep apnea, in which a person has one or more pauses in breathing or shallow breaths while sleeping. Around 25 million Americans suffer from sleep apnea,[1066] which can increase a person's risk for heart failure, stroke, obesity, diabetes, and high blood pressure.[1067] NIH's research on pulmonary diseases seeks to disentangle the complex biological underpinnings of these and other conditions, understand who is afflicted by them and why, and treat and prevent their occurrence.

Advancing Chronic Obstructive Pulmonary Disease Research

COPD is a debilitating lung condition that affects one in eight Americans 45 and older. More than 16 million Americans have been diagnosed with COPD, and millions more have it but do not know it. The COPD National Action Plan is the first-ever blueprint for a multifaceted, unified fight against this disease. Developed with input from the broad COPD community (patients, caregivers, federal agencies, nonprofits, researchers, policymakers, industry representatives, and advocates) the Action Plan describes how the community can all work together to raise awareness about COPD and reduce its impact.[1068] In 2021, NHLBI launched an online tracking system to enable all partners to track and share progress. A major priority is to reduce the burden of COPD in rural and underserved communities, in part by improving the use of

[1061] Knudsen NH, et al. *Science* 2020 May 1;368(6490):eaat3987. PMID: 32355002.
[1062] Reddy A, et al. *Cell* 2020 Oct 1;183(1):62-75.e17. PMID: 32946811.
[1063] https://www.niddk.nih.gov/news/archive/2019/metabolism-memory-role-of-insulin-on-the-brain
[1064] Soto M, et al. *Proc Natl Acad Sci U S A* 2019 Mar 26;116(13):6379-6384. PMID: 30765523.
[1065] https://www.cdc.gov/copd/index.html
[1066] https://aasm.org/rising-prevalence-of-sleep-apnea-in-u-s-threatens-public-health/
[1067] https://www.nhlbi.nih.gov/health/sleep-apnea\
[1068] https://www.nhlbi.nih.gov/health-topics/education-and-awareness/COPD-national-action-plan

pulmonary rehabilitation (PR). Although PR is associated with lower mortality from COPD, less than four percent of eligible patients use it.[1069]

COPD was also the fourth leading cause of death and third leading cause of disability in the U.S. in 2018,[1070] and has a disproportionate impact on rural communities. One high priority action is finding new ways to increase the use of PR for COPD patients, especially in rural areas. Despite proven benefits, a very small proportion of COPD patients receive PR during hospitalization, and of those, only about four percent adhere to it after discharge, perhaps due to the challenge of regular travel to distant PR facilities. One group of NHLBI-supported researchers is testing the effectiveness of a home-based PR program that includes a health coach, while another group is analyzing the records of Medicare beneficiaries to identify factors and strategies that enable some hospitals to achieve higher rates of PR participation than others.[1071] These and similar studies should help identify strategies to improve the quality of life for people with COPD.

While smoking is the biggest known risk factor for COPD, one in four people with the disease have never smoked, presenting a large need to identify other risk factors. NIH-funded investigators continue to make progress unraveling the complex causes of chronic COPD. Recently, NHLBI-supported researchers addressed this mystery by analyzing lung scans from 6,529 smoking and non-smoking adults with COPD. They found that people with small airways relative to lung size were more likely to have the disease, even if they did not smoke or have other risk factors.[1072] This growing knowledge about early risk factors and signs of COPD should enable improved identification of at-risk people, earlier treatment, and better outcomes.

Researchers at NIEHS and their collaborators found that inhaling unfragmented hyaluronan improves lung function in patients suffering from severe exacerbation of COPD (patients requiring a breathing apparatus). Hyaluronan, a sugar secreted by living tissue that acts as a scaffold for cells, is also used in cosmetics as a skin moisturizer and as a nasal spray to moisturize lung airways. Utilized as a COPD treatment, hyaluronan shortened the amount of time COPD patients needed breathing support in intensive care, decreased their number of days in the hospital, and saved money by shortening their hospital stay.[1073,1074] The next step is to study this treatment in more patients to understand the optimal conditions and dosing that will produce the most benefit.

Vaping, Electronic Cigarettes, and Conventional Cigarettes Negatively Affect Health

Electronic (e-)cigarettes, which became available to U.S. consumers in 2007, work by heating liquids that typically contain nicotine and other additives to produce a smokeless aerosol that is inhaled into the lungs. E-cigarette use, or vaping, was steadily embraced as a healthy alternative to conventional

[1069] Lindenauer PK, et al. *JAMA* 2020 May 12;323(18):1813-1823. PMID: 32396181
[1070] Xu JQ, et al. Mortality in the United States, 2018. NCHS Data Brief, Number 355. Hyattsville, MD: National Center for Health Statistics; 2020.
[1071] Spitzer KA, et al. *Ann Am Thorac Soc* 2019 Jan;16(1):99-106. PMID: 30417670.
[1072] Smith BM, et al. *JAMA* 2020 Jun 9;323(22):2268-2280. PMID: 32515814.
[1073] https://www.niehs.nih.gov/news/newsroom/releases/2021/february1/index.cfm
[1074] Galdi F, et al. *Respir Res* 2021 Feb 1;22(1):30. PMID: 33517896.

cigarettes, especially among young people. Although multiple factors influence youth initiation and use of tobacco products by 2019, more than one in four high-schoolers reported having vaped in the past 30 days.[1075] In the spring of 2019, the health risks of vaping came into focus when reports began to emerge of e-cigarette or vaping use-associated lung injury (EVALI). By November 2019, CDC data had linked many EVALI cases to use of vaping liquids containing tetrahydrocannabinol (THC), the active ingredient in marijuana, as well as vitamin E acetate, an agent used to dilute THC.[1076] NHLBI-funded researchers quickly pursued these leads, and in February 2020, reported that e-cigarette vapor containing vitamin E acetate causes lung injury in mice similar to that seen in EVALI patients.[1077] These strong links between vitamin E acetate and EVALI led the FDA to advise that vitamin E acetate should not be used in vaping products.

E-cigarette use is typically associated with damage to the lungs. This was highlighted by a small outbreak of E-cigarette associated lung injury in late 2019. Similar to conventional cigarettes, e-cigarette aerosol can also affect many different regions of the body, including potentially the brain. NIEHS-funded researchers exposed mice to either the equivalent of secondhand e-cigarette aerosol or a five-fold higher level for two months. They then measured levels of 15 different metals in brain and other central nervous system (CNS) tissues, such as the spinal cord. Mice exposed to e-cigarette aerosol had a significant buildup of several metals in the brain and CNS. Many of the metals that accumulated in exposed mice were known neurotoxins, including chromium, copper, iron, and lead.[1078,1079] If confirmed in human studies, these results suggest that exposure to e-cigarette aerosol may potentially increase the risk of neurodegenerative disease for both e-cigarette users and bystanders.

The TRSP coordinates the trans-NIH collaboration with the FDA Center for Tobacco Products (CTP) to conduct research supporting FDA regulation of tobacco products, including e-cigarettes.[1080] The Tobacco Centers of Regulatory Science (TCORS) are the centerpiece of this partnership. First funded in 2013, the NIH and FDA renewed their commitment to the TCORS program in 2018, committing more than $151 million in total funding to support nine specialized centers for the next five years. The awards are administered by NCI, NIDA, and NHLBI. TRSP research aims to advance scientific understanding of tobacco product toxicity, addiction, health effects, behaviors, communication, marketing, and the impact of potential FDA regulations, as well as provide rapid-response findings on time-sensitive research topics.[1081] What scientists learn about tobacco through the TCORS program helps inform and assess FDA's prior, ongoing, and potential regulatory activities. TCORS investigators also have the flexibility and capacity to respond to FDA's research needs as issues are raised. Collaborations like TRSP help ensure that FDA has access to the most recent and most accurate biomedical information available.

[1075] Miech R, et al. *N Engl J Med* 2019 Oct 10;381(15):1490-1491. PMID: 31532955.
[1076] Centers for Disease Control and Prevention. *Evaluation of Bronchoalveolar Lavage Fluid from Patients in an Outbreak of E-cigarette, or Vaping, Product Use–Associated Lung Injury — 10 States, August–October 2019*. 2019. https://www.cdc.gov/mmwr/volumes/68/wr/mm6845e2.htm
[1077] Bhat TA, et al. *N Engl J Med* 2020 Mar 19;382(12):1175-1177. PMID: 32101656.
[1078] https://factor.niehs.nih.gov/2021/9/papers/dert/index.htm#a1
[1079] Re DB, et al. *Environ Res* 2021 Nov;202:111557. PMID: 34245728.
[1080] https://prevention.nih.gov/tobacco-regulatory-research
[1081] https://www.fda.gov/tobacco-products/research/tobacco-centers-regulatory-science-tcors

Better Understanding How Air Pollution Contributes to Lung Diseases and Conditions

Although outdoor air quality has improved a lot since the 1990s, many challenges remain in protecting Americans from air quality problems including fine particulate matter (PM). Fine particles, called $PM_{2.5}$ (for their size of 2.5 microns, or roughly 30-times smaller than the thickness of a human hair), are more dangerous because they can penetrate deep into the lungs or even into the blood. Exposure to $PM_{2.5}$ particles is associated with lung and throat irritation, trouble breathing, lung cancer, and other non-pulmonary issues including eye irritation and heart attack (in people with heart disease).[1082] NIEHS-supported researchers examined the relationship between lung function test results, self-reported nonsteroidal anti-inflammatory drug (NSAID) use, and ambient PM and black carbon (PM from burning fossil fuels) exposure in a cohort of older men (average age of 73). They found that the use of any NSAID, but mainly aspirin, nearly halved the effect of PM on lung function. While the biological mechanism is unknown, the researchers speculate that NSAIDs mitigate inflammation brought about by air pollution.[1083, 1084]

Researching Treatments for Lung Diseases

Pulmonary fibrosis (PF) occurs when lung tissue becomes damaged and scarred. This thickened, stiff tissue makes it more difficult for the lungs to work properly and leads to shortness of breath. If the condition is severe, a very minor exertion, such as walking up a single flight of stairs, is all it takes to become winded. Many cases of PF do not have a clear cause, treatment options are very limited, and therapies to ease symptoms and improve quality of life do not work for everyone. NHLBI is supporting precision medicine approaches to overcome these challenges. Current projects focus on developing better model systems to understand disease progression and to conduct preclinical studies of potential new therapies. Earlier retrospective analysis of PF patients suggested that a gene involved in regulating inflammation, called *TOLLIP* that codes for the Toll interacting protein (TOLLIP), influences PF patient's responses to an antioxidant drug treatment called N-acetylcysteine (NAC). The new NHLBI-supported Prospective tReatment EffiCacy in IPF uSlng genOtype for Nac Selection (PRECISIONS) trial will enroll only those patients who carry the *TOLLIP* gene variation to determine if they benefit from NAC treatment.[1085] Since NAC is already approved for other conditions, if the PRECISIONS trial is successful, PF patients may have a new therapy option in the near future.

Systemic sclerosis (SSc), commonly known as scleroderma, is a rare autoimmune disease associated with vasculopathy (damaging of blood vessels), inflammation, and fibrosis (scarring or hardening) of the skin and/or internal organs, including the lungs. Systemic scleroderma associated interstitial lung disease (scarring of lungs) (SSc-ILD) is largely irreversible and is the leading cause of mortality and morbidity among SSc patients. NIAMS-supported researchers evaluated a recently completed phase 3 clinical trial[1086] and found that 48 weeks of tocilizumab (immunosuppressive drug) treatment stabilized lung function in patients with SSc-ILD. Importantly, tocilizumab preserved lung function regardless of baseline

[1082] https://www.cdc.gov/air/particulate_matter.html
[1083] https://www.publichealth.columbia.edu/public-health-now/news/aspirin-may-prevent-air-pollution-harms
[1084] Gao X, et al. *Am J Respir Crit Care Med* 2020 Feb 1;201(3):374-378. PMID: 31553629.
[1085] https://reporter.nih.gov/project-details/9822535
[1086] https://clinicaltrials.gov/ct2/show/study/NCT02453256

lung function and fibrosis severity before the treatment.[1087] This means that patients with early stage diffuse cutaneous SSc, a form of the disease associated with a high prevalence of lung disease, could benefit greatly from tocilizumab treatment to potentially prevent disease progression.

Improving Diagnostics and Better Understanding Risk Factors

Interstitial lung disease (ILD), or fibrosis (scarring) of the lungs, causes stiffness which makes it difficult to breathe and get oxygen to the bloodstream. Since lung damage from ILD is often irreversible and gets worse over time, it is important to diagnosis ILD early. Pulmonary function tests are commonly used to screen for ILD in patients with SSc; however, those tests have low sensitivity, meaning that too many cases are missed. A NIAMS-supported clinical study demonstrated that adding high-resolution computed tomography (HRCT) scans as an additional screening tool alongside pulmonary function testing improves ILD diagnosis among patients with early stage diffuse cutaneous SSc.[1088] Based on this report, all patients with diffuse cutaneous SSc are recommended to undergo baseline HRCT imaging for better ILD diagnosis, even among patients whose pulmonary function tests are in the normal range.

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease, in which the immune system attacks healthy cells within the body by mistake, that causes inflammation (painful swelling), mainly in the joints. Inflamed airways of the upper lungs are hypothesized to contribute to development of RA, supported by the observation that smoking is the strongest environmental RA risk factor, but the link between the two is still unclear. NIAMS-supported researchers demonstrated that individuals with lung diseases such as asthma and COPD are more likely to develop RA.[1089] These findings have implications in informing the clinical care of asthma and COPD patients to allow for early detection of RA and lowering the risk of negative long-term outcomes. They also point to the need for more research to understand the biological connections between lung diseases and the development of RA so that new treatment options can be developed.

Substance Misuse and Addiction

A range of substances, including nicotine, cannabinoids, alcohol, opioids, depressants, stimulants, and hallucinogens, continue to be misused, leading to addiction for many people. According to the 2021 National Survey on Drug Use and Health (NSDUH), 57.8 percent of Americans (or 161.8 million people) aged 12 or older reported substance use in the past month, 16.5 percent (46.3 million people) aged 12 or older had an alcohol or illicit drug substance use disorder (SUD) in the past year, and 3.3 percent (or 9.2 million people) aged 12 or older misused opioids in the past year.[1090] Individuals living with SUDs are at particular risk for developing comorbid chronic health conditions, including chronic pain,[1091] cancer, and heart disease.[1092] In 2021, among people with mental illness, 33.5 percent had a SUD, and among adults

[1087] Roofeh, et al. *Arthritis Rheumatol* 2021 Jul;73(7):1301-1310. PMID: 33538094.
[1088] Bernstein EJ, et al. *Arthritis Rheumatol* 2020 Nov;72(11):1892-1896. PMID: 32583956.
[1089] Ford JA, et al. *Arthritis Rheumatol* 2020 May;72(5):704-713. PMID: 32129572.
[1090] Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health. 2022. https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report
[1091] Garland EL, et al. *Neuroscience & Biobehavioral Reviews*. 2013;37(10):2597-2607. PMID: 23988582.
[1092] Schulte MT and Hser YI. *Public Health Reviews*. 2013;35(2). PMID: 28366975.

with SUD, 44 percent had a mental illness.[1093] In the U.S., the annual economic cost of substance misuse is estimated to be hundreds of billions of dollars in lost productivity, health care costs, and costs associated with involvement in the criminal justice system.[1094] Despite affecting tens of millions of people each year and contributing to lost productivity and increased morbidity and mortality, in 2021 only 6.3 percent of people aged 12 or older who had a SUD in the past year received any treatment.[1095] Although many challenges remain, groundbreaking research and discoveries about the brain have revolutionized how alcohol and drug addictions are understood and treated. ICOs across NIH use knowledge gleaned from decades of research as a guide to shaping future directions in research and dissemination activities regarding substance misuse and addiction.

NIDA is the lead federal agency for research on drug abuse, though several ICOs across NIH focus on aspects of substance misuse and addiction. NIDA engages in and supports efforts to advance the science on the biological, environmental, behavioral, and social causes of drug use and addiction and to apply that knowledge to improve individual and public health. This work includes detecting and responding to emerging drug misuse trends and understanding how drugs work in the brain and body, as well as developing and testing new approaches to treatment and prevention. NIDA also supports research training, career development, public education, public-private partnerships, and research dissemination efforts.

Opioid Misuse and Opioid Use Disorders

NIH continues to engage in activities to better understand, prevent, and treat opioid misuse and opioid use disorder (OUD). Between FY 2019 and FY 2021, collaborations within NIH and with other federal agencies were established to meet the needs of high-risk populations, enhance clinical trial networks, optimize treatments, and foster innovative and timely research to address the opioid crisis.

The HEAL Initiative is an NIH-wide effort to respond to the opioid public health crisis in the U.S. HEAL supports research aimed at advancing new therapeutics to address OUD, developing new prevention and treatment strategies, improving the implementation and dissemination of existing treatments, and enhancing care for infants exposed to opioids. In 2019, the NIH HEAL Initiative announced a $945 million investment for research on pain management and on treatments for opioid misuse and addiction.[1096] In concert with this announcement, NIH launched the HEAL website to be a hub for funding and program information, data, project descriptions, related news and events, and resources.

[1093] SAMHSA National Survey on Drug Use and Health: https://www.samhsa.gov/data/sites/default/files/reports/rpt39441/NSDUHDetailedTabs2021/NSDUHDetailedTabs2021/NSDUHDetTabsSect6pe2021.htm

[1094] https://nida.nih.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/frequently-asked-questions/drug-addiction-treatment-worth-its-cost

[1095] Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2021 National Survey on Drug Use and Health.* 2022. https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021NSDUHFFRRev010323.pdf

[1096] https://archives.nida.nih.gov/news-events/noras-blog/2019/09/nida-announces-new-nih-heal-initiative-awards-to-address-opioid-crisis

NIH and the Substance Abuse and Mental Health Services Administration launched the HEALing Communities Study® to investigate which approaches for preventing and treating opioid misuse and OUD are most effective at the local level. This multi-site research study is developing and testing strategies to help communities deploy evidence-based strategies to reduce opioid-related overdose fatalities. An integral feature of the study's design is to test the impact of engaging state and local governments, as well as community groups such as police departments, faith-based organizations, and schools. The study will also look at the effectiveness of coordinated systems of care designed to increase the number of individuals receiving medication to treat OUD, increase the distribution of naloxone (a medicine that rapidly reverses an opioid overdose), and reduce high-risk opioid prescribing. The HEALing Communities Study also provides a unique opportunity to understand the consequences of the intersection of COVID-19 and the opioid epidemic in rural and urban communities.[1097]

The Justice Community Opioid Innovation Network (JCOIN) is a NIDA initiative to advance scientific knowledge on effective policies, practices, and interventions, and to expand their use in daily practice within health and justice settings.[1098] With support from the NIH HEAL Initiative, JCOIN investigates approaches to increase high-quality care for people with opioid misuse and OUD in justice settings. JCOIN consists of a network of research investigators and interested parties who work together to rapidly conduct studies on quality care for opioid misuse and OUD in justice system populations by facilitating partnerships between local and state justice systems and community-based treatment providers. JCOIN projects include a national survey of addiction treatment delivery services within the justice system, studies on the effectiveness and adoption of new medications, prevention and treatment interventions, and technologies, and using existing data sources in novel ways to understand care in justice populations.

Mobile health clinics are used in a variety of locales to increase accessibility to health care and address disparities in a cost-effective manner.[1099] In 2021, the NIDA and NIAID-supported INTEGRA study was launched to determine whether delivering integrated health services through mobile clinics can improve HIV and substance use outcomes among people with OUD who inject drugs.[1100] The study is a clinical trial with sites in Los Angeles, New York, Houston, Philadelphia, and Washington, D.C. If effective, this mobile clinic model could serve as an example of a strategy for expanding access to care and providing uninterrupted treatment to an underserved population by addressing the linked public health crises of addiction and HIV.

[1097] Chandler RK, et al. *Drug and Alcohol Dependence*. 2020;217:108329. PMID: 33075691.
[1098] https://heal.nih.gov/research/research-to-practice/jcoin
[1099] Yu SWY, et al. *International Journal for Equity in Health*. 2017;16(1). PMID: 28982362.
[1100] https://nida.nih.gov/news-events/news-releases/2021/06/nih-funded-study-tests-one-stop-mobile-clinics-to-deliver-hiv-substance-use-care

Figure 28: One of five mobile health clinics deployed for the NIH-funded INTEGRA study. Credit: Image Courtesy of LifelineMobile®. Artwork for the clinic was designed by artist Shepard Fairey

Drug addiction is often a relapsing disease, with relapse rates similar to other chronic diseases.[1101] In 2021, NIDA and the NIH HEAL Initiative established Research Recovery Networks to bring together critical partners (including researchers, payors, providers, people in recovery) and advance the science of long-term recovery from OUD.[1102] By the end of FY 2021, five institutions received funding to support these projects. Collectively, projects under this program are developing resources to support recovery research with a focus on community-based recovery centers, justice-involved youth, family-based recovery, recovery in rural settings, and integrated networks of care.

In FY 2020, the NIH HEAL Initiative along with OBSSR, NIAMS, NIDCR, NIDDK, NIDA, NINDS, NCCIH, and NCI, supported supplements to current awards to address continued challenges patients experienced due to stigma, discrimination, or prejudice in the context of pain management, opioid use, and/or OUD and its treatment.[1103] A total of $1.7 million was made available to supplement eight existing HEAL Initiative awards and cooperative agreements to evaluate strategies for reducing stigma and improving treatment, management, and services for people with chronic pain and/or OUD.

NIDA's Clinical Trials Network (CTN) facilitates collaboration among researchers, medical and treatment providers, patients, and NIH staff to develop, test, and implement new addiction treatments. However, the ongoing opioid crisis presents an urgent public health need to quickly expand the CTN. The HEAL Initiative and NIDA supported the enhancement of the CTN's ability to use cutting-edge research designs, methods, and data resources to address opioid use in areas of the U.S. most affected by the opioid crisis.[1104] The expanded network has contributed to broad-reaching changes in medical practice, including the use of buprenorphine as a medication treatment for OUD. The CTN also strengthened the capacity to conduct trials by adding new sites and new investigators, expanded existing studies in the network and

[1101] McLellan AT, et al. *JAMA*. 2000;284(13):1689. PMID: 11015800.
[1102] https://heal.nih.gov/research/research-to-practice/research-recovery-network
[1103] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-101.html
[1104] https://heal.nih.gov/research/research-to-practice/enhancing-clinical-trials-network

initiated research with new investigators in new locations and settings that are impacted by the opioid crisis, facilitated the development and implementation of new studies to improve access to high-quality addiction treatment, and created new opportunities for clinical and research training.

The CTN, with support from the NIH HEAL Initiative, is also testing the efficacy of the Subthreshold Opioid Use Disorder Prevention (STOP) intervention in primary care settings.[1105] STOP adopts an early intervention approach based on a collaborative care model and consists of a practice-embedded nurse care manager who provides patient education and supports the primary care provider in engaging, monitoring, and guiding patients who have risky opioid use, brief advice delivered to patients by their primary care provider, and phone counseling by behavioral health providers to motivate patients and support behavior change.

Emergency departments sporadically use a high-dose buprenorphine induction strategy for the treatment of OUD in response to the increasing potency of illicit opioids and delays in access to follow-up care. To compare outcomes from high dose induction versus a standard lower-dose induction, NIDA and HEAL Initiative-funded researchers conducted a retrospective EHR review of adults with OUD who received buprenorphine in a large, urban emergency department. The researchers reported that high-dose buprenorphine induction in emergency departments was safe and well-tolerated in people with OUD experiencing withdrawal symptoms, making this a potentially promising approach to help people transition to outpatient treatment.[1106,1107]

Patients who remain on medication treatment for OUD for a longer time tend to have better outcomes.[1108] The HEAL Initiative and NIDA funded three institutions to test strategies to improve retention in medication-based treatment for OUD, as well as strategies to improve outcomes among patients who have been stabilized on OUD medications and want to stop taking medication.[1109] These projects will also identify patient characteristics associated with relapse after discontinuation and develop a predictive risk model for relapse. Study findings will help researchers better understand which factors predict relapse and inform the development of tools to assess those factors in patients. If tested strategies are effective, they could be widely and sustainably disseminated and could reduce the public health impact of OUD by improving the delivery of medication-based treatments.

Over 25 million people in the U.S. experience pain every day and need safe, non-addictive treatments to alleviate the pain.[1110] This clinical demand is of importance given that overprescribing of opioids for managing acute and chronic pain has fueled the current epidemic of OUD and overdose deaths. Further, the effectiveness of opioids for long-term pain management is being questioned. NCATS established A

[1105] https://heal.nih.gov/research/new-strategies/prevent-progression
[1106] Herring AA, et al. *JAMA Network Open*. 2021;4(7):e2117128. PMID: 34264326.
[1107] https://nida.nih.gov/news-events/news-releases/2021/07/emergency-department-administered-high-dose-buprenorphine-may-enhance-opioid-use-disorder-treatment-outcomes
[1108] https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2020/12/medications-for-opioid-use-disorder-improve-patient-outcomes
[1109] https://heal.nih.gov/research/new-strategies/duration-retention-discontinuation
[1110] https://www.nccih.nih.gov/research/estimates-of-pain-prevalence-and-severity-in-adults-united-states-2012.

Specialized Platform for Innovative Research Exploration (ASPIRE) to aid in the discovery and development of novel and effective treatments by making the process faster and more cost-effective.[1111] The ASPIRE Design Challenges prize competition, supported by the NIH HEAL Initiative®, sought proposals for innovative and catalytic approaches toward solving the opioid crisis through the development of next-generation addiction-free analgesics. Following its design challenges, NCATS introduced the 2020 ASPIRE Reduction-to-Practice Challenge, which aimed to spur the development of a comprehensive integrated platform for translational innovation in pain, OUD, and overdose.[1112,1113]

NIDA supports research to evaluate the safety and efficacy of novel and re-purposed pharmacotherapies and devices to treat SUDs. This work spans all phases of medical product development, including synthesis and preclinical evaluation of potential therapeutics, clinical trial design and execution, and preparing regulatory submissions to the FDA. In 2020, NIDA-supported researchers began developing small molecule *sequestrants* that are designed to rapidly reverse drug overdoses by binding to drug molecules in the blood and accelerating their removal from the body through urine.[1114] NIDA also funded the development of new longer-acting overdose-reversal medications to more effectively reverse overdose from synthetic opioids such as fentanyl. This research included the development of an intranasal formulation of nalmefene.[1115] Through NIH HEAL Initiative funding, NIDA is accelerating the availability of novel treatments for OUD and overdose by developing longer-acting formulations of existing OUD drugs including buprenorphine and methadone. Existing treatments for novel applications are also being tested, such as the insomnia treatment suvorexant, which is being tested for its ability to improve sleep and address other withdrawal symptoms in people with OUD.[1116,1117,1118]

Methadone, buprenorphine, and naltrexone are approved by the FDA for the treatment of OUD, and lofexidine is approved to treat opioid withdrawal. Naloxone can effectively reverse opioid overdose, but reversing respiratory arrest caused by drug combinations or powerful synthetic opioids can require multiple doses. In response to the need for more flexible treatment options, the NIH HEAL Initiative, NIDA, NIAID, and NIAAA support the Focusing Medication Development to Prevent and Treat Opioid Use Disorder and Overdose Program, which includes a series of targeted studies that has exceeded the goal of 15 investigational new drug applications and five new drug applications to the FDA for the prevention and treatment of OUD and overdose.[1119] Between 2019 and 2021, there were over 70 awards to accelerate the discovery and development of novel medications to treat all aspects of the opioid addiction cycle, including progression to chronic use, withdrawal symptoms, craving, relapse, and overdose.

[1111] https://ncats.nih.gov/aspire
[1112] https://ncats.nih.gov/aspire/funding/challenges
[1113] https://ncats.nih.gov/aspire/funding/2020Challenge
[1114] https://reporter.nih.gov/project-details/10390959
[1115] Krieter P, et al. *J. of Pharmacology and Experimental Therapeutics*. 2019;371(2):409-415. PMID: 30940694.
[1116] Compton WM and Volkow ND. *JAMA Network Open*. 2021;4(5):e219708. PMID: 33970262.
[1117] https://nida.nih.gov/news-events/news-releases/2021/05/long-lasting-medications-may-improve-treatment-satisfaction-in-people-with-opioid-use-disorder
[1118] Huhn AS, et al. *Science Translational Medicine*. 2022;14(650). PMID: 35731889.
[1119] https://heal.nih.gov/research/medication-options/focusing-development

While there are effective medications available for the treatment of OUD, many people seeking help in the U.S. only receive counseling, drug testing, peer support, or education. In 2020, NIDA-supported researchers analyzed treatment data and state death records of patients with OUD and reported that among nearly 50,000 adults receiving outpatient treatment, fewer overdose deaths occurred among those treated with opioid agonist medications than among those treated with non-medication approaches.[1120] In addition, a longer time on medication treatment was associated with a lower risk of overdose death after discharge. Study results may be helpful for the development of more patient-centered care for OUD that includes medication, non-medication treatment, and improved retention in care.

Medication-based treatment is an established and effective intervention for people with OUD, however, the people who would benefit from these medications often do not receive them or stay on them only a short time, which limits chances for long-term recovery. Through the NIH HEAL Initiative, and with support from NCCIH and NIDA, the Behavioral Research to Improve Medication-Based Treatment Program was established to support research that assesses whether behavioral interventions can improve outcomes of medication-based treatment.[1121] Between 2019 and 2021, 11 grants were funded to test the effectiveness of combining medications with a wide range of evidence-based behavioral interventions in diverse groups of patients. The behavioral interventions under study include yoga and mindfulness, cognitive behavioral therapy, multidisciplinary rehabilitation, and mobile health technology. Researchers hope to determine whether using these interventions in combination with medication improve treatment outcomes and adherence to medication, and whether combined therapies reduce relapse in individuals seeking treatment for OUD.

NIDA is supporting efforts to develop monoclonal antibodies to target fentanyl and prevent it from entering the brain. The immune system uses antibodies to identify foreign or harmful molecules before binding and marking them for elimination from the body or for destruction. Following NIDA-funded studies, the monoclonal antibody IXT-m200 has received Fast Track designation from the FDA.[1122] Opioid vaccines, which can be made by attaching pharmacologically inactive opioid molecules to proteins or viral particles that trigger antibody production, are another kind of emerging immunotherapy. As part of the NIH HEAL Initiative, NIDA is supporting the first-ever phase 1 clinical trial of a vaccine against opioids.[1123]

Sleep deficiency, including sleep disorders (e.g., insomnia, sleep apnea), circadian disruption (e.g., delayed sleep phase and jet lag), and poor sleep quality (e.g., sleep fragmentation, impaired sleep architecture), is present in greater than 75 percent of patients with OUD.[1124,1125] By the end of FY 2020, through the NIH HEAL Initiative and support from NIDA and NHLBI, eight institutions received awards to conduct basic and clinical research to identify the behavioral and molecular mechanisms that directly connect sleep to the

[1120] Krawczyk N, et al. *Addiction*. Published online February 24, 2020. PMID: 32096302.
[1121] https://heal.nih.gov/research/research-to-practice/brim
[1122] https://nida.nih.gov/news-events/nida-notes/2020/01/part-1-immunotherapies-new-tool-to-treat-methamphetamine-addiction
[1123] https://heal.nih.gov/news/stories/OUD-vaccine
[1124] Langstengel J and Yaggi HK. *Clinics in Chest Medicine*. 2022;43(2):e1-e14. PMID: 35659031.
[1125] Fathi HR, et al. *Addict Health*. 2020 Apr;12(2):140-158. PMID: 32782736.

biological underpinnings of OUD.[1126] Projects include research on how sleep and circadian rhythms are related to opioid addiction, withdrawal, relapse, and response to medication treatment. Some projects involve experimental models of sleep and circadian deficiency and OUD, including behavioral, pharmacological, and genetic models. Researchers will use an array of approaches, such as in vivo, in vitro, genomic, imaging, pharmacologic, and computational strategies, to study behavioral, physiological, molecular, genetic, and pharmacological mechanisms that combine sleep and OUD.

There is an urgent need to identify effective approaches to treat people who have OUD and co-occurring mental health condition(s). Estimates from the 2021 NSDUH suggest that among adults aged 18 or older, those with any mental illness in the past year were more likely than those without mental illness in the past year to misuse opioids (i.e., using illegal opioids or using legal opioids other than as prescribed).[1127] During FY 2021, the NIH HEAL Initiative and NIDA funded 13 awards to develop, optimize, and test approaches to improve delivery of treatments and services for people with co-occurring OUD, mental illness, and/or suicide risk.[1128] Researchers funded through the Optimizing Care for People with Opioid Use Disorder and Mental Health Conditions program are working to develop screening methods to identify people who have OUD and co-occurring mental health disorders and assess the cost, effectiveness, and sustainability of collaborative care strategies. A focus is placed on leveraging strong research-practice partnerships and on harnessing the expertise of interdisciplinary teams for the diagnosis and treatment of OUD and mental health disorders.

There are a multitude of risk factors for opioid misuse or addiction, including past or current substance misuse, untreated psychiatric disorders, childhood adversity, pre-adolescent sexual abuse, young age, and social or family environments that encourage misuse.[1129] The NIH HEAL Initiative, NCCIH, NIDA, and NIMH supported several research awards to study prevention strategies for at-risk youth transitioning into adulthood. There is a special focus on vulnerable populations with increased risk of SUDs, such as American Indian/Alaska Native (AI/AN) and Black communities.[1130] Funding for a coordinating center, 27 research grants and five supplemental awards were also provided to facilitate the inclusion of social network characteristics into existing AI/AN studies that address substance use and/or mental health.[1131] Researchers are also working to develop and test effective strategies to prevent opioid misuse and OUD among vulnerable populations, including older adolescents, young adults, and AI/AN communities. The studies seek to expand knowledge of characteristics that increase risk for opioid misuse or confer protection, as well as related behavioral health and drug use outcomes, including suicide. A focus will also be placed on developing strategies for settings that can identify and reach at-risk individuals and populations, such as health care, justice, school, and child welfare systems.

[1126] https://heal.nih.gov/research/new-strategies/sleep-dysfunction

[1127] Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health.* 2020. https://www.samhsa.gov/data/

[1128] https://heal.nih.gov/research/new-strategies/optimizing-care

[1129] Webster LR. *Anesthesia & Analgesia*. 2017;125(5):1741-1748. PMID: 29049118.

[1130] https://heal.nih.gov/research/new-strategies/preventing-opioid-use-disorder

[1131] https://heal.nih.gov/research/new-strategies/preventing-opioid-use-disorder

NCATS supports and facilitates a variety of funding and collaboration opportunities designed to address the opioid crisis, including pain management. Using NCATS' Clinical and Translational Science Awards Trial Innovation Network, the NIH HEAL Pain Management Effectiveness Research Network is supporting studies that compare the effectiveness of therapies to prevent or manage pain in ways that reduce the risk of addiction.[1132,1133,1134] The goal is to provide clinicians with information about the effectiveness of treatments or management strategies that reduce opioid use and pain associated with many types of diseases or conditions.

There is an increasing prevalence of prescription opioid use among pregnant women. In response, NICHD-funded researchers conducted a retrospective study to better understand the effects of maternal opioid use on neurodevelopmental disorders in early childhood. The aim of this study was to quantify the association between prenatal opioid exposure from maternal prescription use and neurodevelopmental outcomes in early childhood.[1135] The researchers looked at health insurance records of infants born between 2010 and 2012 to mothers with no history of opioid misuse and to mothers with drug dependence. Overall, children whose mothers had been prescribed opioids during pregnancy did not have a higher incidence of neurodevelopmental disorders in early childhood. However, children whose mothers received a particularly high total dose or who were prescribed opioids for extended periods of time (a total of 14 days or longer) were more likely to develop neurodevelopmental disorders in early childhood, compared to children whose mothers had not been prescribed opioids during pregnancy.

Newborns exposed to addictive substances in the womb are risk for neonatal abstinence syndrome (NAS), or more specifically in the case of opioids, neonatal opioid withdrawal syndrome (NOWS). NAS/NOWS symptoms include tremors, excessive crying and irritability, and problems with sleeping, feeding, and breathing. From 2010 to 2017, the estimated rate of NAS increased from 4.0 to 7.3 per 1,000 birth hospitalizations.[1136] The NIH HEAL Initiative, NIDA, and NICHD funded several institutions to support the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) Program, which aims to inform the clinical care of infants who are exposed to opioids in the womb. The ACT NOW Eat, Sleep, Console Clinical Trial is a strategy to treat infants with NOWS that prioritizes non-pharmacologic care over the use of opioids, and will compare infant outcomes before and after Eat, Sleep, Console was implemented in hospitals. The ACT NOW Trial to Shorten Pharmacologic Treatment of Newborns with NOWS (Weaning Trial) will compare rapid with slow opioid weaning management among neonates treated with morphine or methadone. The ACT NOW Longitudinal Study will look at MRI findings and other data in infants with and without NOWS to examine the impact of antenatal opioid exposure and NOWS on childhood brain structure and connectivity. In the next phase of the ACT NOW program, investigators will plan and conduct a multi-center, randomized controlled clinical trial that further investigates how to optimize care for infants exposed to opioids in utero.

[1132] https://ncats.nih.gov/heal/funding
[1133] https://www.painconsortium.nih.gov/funding-research/nih-heal-pain-management-ern
[1134] https://trialinnovationnetwork.org/heal-pain-ern-other-heal-foas/
[1135] Wen X, et al. *Drug Safety*. Published online June 7, 2021. PMID: 34100263.
[1136] Hirai AH, et al. *JAMA*. 2021;325(2):146. PMID: 33433576.

The first few years of life are a period of exponential growth and brain development. The long-term effects of perinatal exposure to opioids on infant and child development are unknown. In 2019, through the NIH HEAL Initiative and with support from NIDA, NIMH, NINDS, NIAAA, NICHD, NIBIB, NIEHS, and NIMHD, 29 awards were made to support phase 1 of the HEALthy Brain and Child Development (HBCD) Study.[1137] The aim of the HBCD Study is to recruit a large cohort of pregnant women from regions of the country significantly affected by the opioid crisis and follow them and their children through early childhood. In late 2021, 27 sites were funded as part of phase 2 of the HBCD Study. Phase 2 studies will support the collection of data that will enable researchers to analyze brain and behavioral development in substance-exposed and non-drug-exposed infants and children across a variety of regions and from diverse demographic backgrounds. Participants' data collection for HBCD Study will begin at birth and continue through early childhood. Structural and functional brain imaging data, anthropometrics, medical history, family history, biospecimens, and indicators of social, emotional, and cognitive development will be collected. Knowledge gained from this research will be used to better understand and ultimately prevent or attenuate the harms of prenatal exposure to drugs or other adverse environmental conditions. Protective factors that may mitigate some of these adverse outcomes will also be identified.

NIDA, with support from the NIH HEAL Initiative, supports research to explore and implement evidence-based interventions to address OUD and overdose via innovative technologies through its SBIR/STTR program. This includes the development of ReSET and ReSET-O, the first FDA-approved mobile applications for behavioral treatment of SUD and OUD.[1138] Another mobile application turns a user's smartphone into a portable respiratory monitor that can detect changes in breathing that are associated with an overdose, prior to sounding an alarm and alerting emergency services.[1139] NIDA, with support from the NIH HEAL Initiative, also supports the development of novel technologies, such as a hospital bassinet pad called Prapela SVS that applies gentle vibrations to soothe babies born dependent on opioids, which received Breakthrough Device designation from the FDA.[1140] Another novel NIDA-funded technology uses virtual reality as an alternative to pain relief from opioids.[1141]

Stimulant Misuse

Overdose deaths involving methamphetamine nearly tripled from 2015 to 2019 among people ages 18-64 in the U.S., with AI/AN populations experiencing the highest death rates, according to two studies by NIDA.[1142,1143] The number of people who reported using methamphetamine during this time did not increase as steeply, but analyses found that populations with methamphetamine use disorder have become more diverse. The studies suggest that increases in higher-risk patterns of methamphetamine use, such as increases in methamphetamine use disorder, frequent use, and use of other drugs at the

[1137] https://heal.nih.gov/research/infants-and-children/healthy-brain
[1138] https://www.fda.gov/news-events/press-announcements/fda-clears-mobile-medical-app-help-those-opioid-use-disorder-stay-recovery-programs
[1139] https://milkeninstitute.org/article/sound-life-sciences-jacob-sunshine
[1140] https://www.inknowvation.com/sbir/story/prapela-earns-fda-breakthrough-device-designation
[1141] https://www.businesswire.com/news/home/20191022005322/en/CORRECTING-and-REPLACING-AppliedVR-Receives-NIDA-Grants-to-Study-Virtual-Reality-as-an-Opioid-Sparing-Tool-for-Pain
[1142] Han B, et al. *JAMA Psychiatry*. Published online September 22, 2021. PMID: 34550301.
[1143] Han B, et al. *JAMA Psychiatry*. 2021;78(5):564. PMID: 33471025.

same time, may be contributing to the rise in overdose deaths. Results underscore the urgent need for new preventative measures and treatment approaches, including safe and effective medications.

The rise in deaths due to overdose from stimulant drugs is now a public health issue, especially since it has been challenging to develop medications to treat stimulant use disorders.[1144,1145] Results from the Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder study, conducted by NIDA's CTN, indicated a breakthrough for a potential medication for methamphetamine use disorder. Researchers found that a combination of oral bupropion and injectable naltrexone successfully reduced methamphetamine use and cravings in a large sample of treatment-seeking people with methamphetamine use disorder, compared to placebo. In addition, once initiated, the effectiveness of the bupropion and naltrexone combination was similar to the effectiveness of analgesics for treating pain and most medical treatments for mental health disorders.[1146] While additional research is needed, the success of this trial is a step toward developing a medication that could be helpful in addressing stimulant use disorders.

Alcohol Misuse and Alcohol Use Disorder (AUD)

Alcohol consumption per capita has increased in the U.S.[1147,1148] NIAAA researchers analyzed yearly death certificate data and reported that the number of death certificates mentioning alcohol more than doubled from 1999 to 2017, a year in which alcohol played a role in 2.6 percent of all deaths in the U.S.[1149] The researchers noted that liver disease and overdoses on alcohol alone or with other substances accounted for nearly half of the alcohol-related deaths in 2017, and that alcohol-related deaths seem to have increased among all age, race, and ethnic groups by the end of the study period. Given previous reports that death certificates often fail to indicate the contribution of alcohol, the researchers postulate that the scope of alcohol-related mortality in the U.S. is likely higher than suggested from death certificates alone.

Alcohol screening is an important step for identifying and preventing alcohol-related problems among youth. NIAAA offers the *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide* to assist health care providers in identifying current alcohol use and alcohol use disorder (AUD) in youth ages 9-18, as well as those at risk for future alcohol use. The Youth 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. In 2019, an NIAAA-supported study demonstrated the predictive validity of the youth guide in accurately characterizing risk for future AUD.[1150] The importance of alcohol screening among youth was also emphasized in another 2019 NIAAA-supported study that found that relative to usual care, adolescents who received alcohol screening, brief intervention, and

---

[1144] Ruhm CJ. *Health Affairs*. 2019;38(7):1216-1224. PMID: 31260365

[1145] https://nihcm.org/publications/stimulant-deaths-on-the-rise-compounded-by-rise-in-synthetic-opioids

[1146] Trivedi MH, et al. *New England Journal of Medicine*. 2021;384(2):140-153. PMID: 33497547.

[1147] Martinez P, et al. *Alcoholism: Clinical and Experimental Research*. 2019;43(3):509-521. PMID: 30742317.

[1148] National Institute on Alcohol Abuse and Alcoholism. *SURVEILLANCE REPORT #113: APPARENT PER CAPITA ALCOHOL CONSUMPTION: NATIONAL, STATE, AND REGIONAL TRENDS, 1977-2017. 2019*. https://www.niaaa.nih.gov/publications/surveillance-reports

[1149] White AM, et al. *Alcoholism: Clinical and Experimental Research*. 2020;44(1):178-187. PMID: 31912524.

[1150] Linakis JG, et al. *Pediatrics*. 2019;143(3):e20182001. PMID: 30783022.

referral to treatment in pediatric primary care settings had improved health, mental health, and substance use outcomes over a three-year follow up period.[1151]

Many people who need treatment for AUD receive no treatment of any kind, and little is known about what sustains longer-term recovery.[1152] NIAAA developed a definition of AUD recovery based on qualitative feedback from key interested parties (e.g., researchers, clinicians, and recovery specialists).[1153] The new definition is viewed as a process of behavioral change and takes into account remission from AUD, cessation from heavy drinking (a non-abstinent recovery outcome), and improvements in dimensions of quality of life and well-being. The definition was formally unveiled in a September 2020 virtual roundtable discussion sponsored by NIAAA that discussed a wide range of topics and challenges related to defining recovery.[1154] Use of the new NIAAA definition of recovery will facilitate more consistent and accurate comparisons of AUD recovery across different research studies and settings.

NIAAA is developing the *Healthcare Professional's Core Resource on Alcohol*, a resource to assist clinicians in providing better care for patients whose alcohol use may be affecting their health.[1155] This resource consists of 14 interconnected articles covering the basics of what every healthcare professional needs to know about alcohol, including foundational knowledge for understanding alcohol-related problems, information about the clinical impacts of alcohol on a broad range of health conditions, and strategies for prevention and treatment. The resource represents a major NIAAA effort toward meeting the need for treatment of alcohol-related problems.

Researchers around the world use a variety of classification systems to categorize individuals who are affected by prenatal alcohol exposure, making it difficult to compare research findings.[1156] Fetal alcohol spectrum disorders (FASDs) are a group of conditions that can occur in a person who was exposed to alcohol before birth, and can include physical problems and problems with behavior and learning. In FY 2020, NIAAA convened a meeting of international experts as a first step towards the development of a single system for classifying the range of FASD subtypes. A new classification system, if developed, would require domains such as neurobehavioral impairment, dysmorphology (changes in physical features), and prenatal alcohol exposure, and be adaptable across the lifespan. Work on a single classification system is underway, and its adoption by researchers worldwide could accelerate progress on the diagnosis, prevention, and treatment of FASD.

Developing culturally appropriate interventions to prevent alcohol-related problems among AI/AN communities is an NIH priority. In the Yup'ik community in Alaska, NIAAA-supported researchers and Yup'ik community leaders collaborated to create and assess culturally compatible preventive

[1151] Sterling S, et al. *Pediatrics*. 2019;143(5):e20182803. PMID: 31018988.
[1152] Kranzler HR and Soyka M. *JAMA*. 2018;320(8):815-824. PMID: 30167705.
[1153] Hagman BT, et al. *American Journal of Psychiatry*. Published online April 12, 2022. PMID: 35410494.
[1154] https://www.niaaa.nih.gov/research/niaaa-recovery-roundtable-proceedings
[1155] https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol
[1156] https://www.niaaa.nih.gov/fetal-alcohol-spectrum-disorders

interventions for AUD and suicide in youth aged 12 to 18 years.[1157] In FY 2021, NIAAA hosted a webinar using this collaborative project as a case study for creating similarly tailored interventions for AI/AN communities across the U.S.[1158] The project utilizes history and culture as organizing principles for substance use prevention efforts with youth in indigenous communities.

Underage and harmful consumption of alcohol continue to pose public health risks. According to the 2019 NSDUH, almost 53 percent of full-time college students ages 18 to 22 drank alcohol in the past month and about 33 percent engaged in binge drinking during that same time frame.[1159] In 2019, NIAAA updated the College Alcohol Intervention Matrix (CollegeAIM),[1160] an easy-to-use tool to help college and university officials identify and compare evidence-based alcohol interventions. The latest version of CollegeAIM includes seven additional interventions and revised ratings for five interventions based on recent research findings. Over 60 alcohol interventions based on cost, effectiveness, and ease of implementation are rated through CollegeAIM. In collaboration with the International Town and Gown Association, NIAAA hosted a series of webinars in 2021 to disseminate updated information about the resource.

Alcohol use is commonly initiated during adolescence, and early alcohol use is linked to a range of short- and long-term consequences, including compromised brain development.[1161] NIAAA launched the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) to conduct a multi-site, longitudinal study on the effects of alcohol exposure on the developing adolescent brain and to identify brain characteristics that may predict AUD and related problems. Through support from NIAAA, NIDA, NIMH, and NICHD, NCANDA researchers found that youth with a history of alcohol use exhibit weakened connections between brain networks involved in the regulation of emotional and cognitive functioning.[1162] NCANDA researchers have also demonstrated that youth who have experienced childhood trauma have disrupted patterns of connections between brain networks that could predict future progression to AUD.[1163] In FY 2021, NIAAA renewed the consortium to characterize more fully and accurately alcohol-related changes in the brain and behavior development across the adolescent years

[1157] https://www.niaaa.nih.gov/news-events/news-releases/nih-project-models-culturally-appropriate-alcohol-use-and-suicide-preventions-youth-alaska-native
[1158] https://www.niaaa.nih.gov/news-events/meetings-events-exhibits/webinar-substance-abuse-prevention-youth-indigenous-communities
[1159] Lipari RN and Jean-Francois B. *A Day in the Life of College Students Aged 18 to 22: Substance Use Facts*. Substance Abuse and Mental Health Services Administration. 2016. https://www.ncbi.nlm.nih.gov/books/NBK396154/
[1160] https://www.collegedrinkingprevention.gov/CollegeAIM/
[1161] Report to Congress on the Prevention and Reduction of Underage Drinking, 2021, The Interagency Coordinating Committee on the Prevention of Underage Drinking, https://www.stopalcoholabuse.gov/media/ReportToCongress/2021/report_main/2021_Report_to_Congress_updated_Oct2022.pdf
[1162] De Bellis MD, et al. Current Addiction Reports. 2020;7(2):99-107. PMID: 32509502.
[1163] Silveira S, et al. Biol Psychiatry Cogn Neurosci Neuroimaging. 2020 May;5(5):499-509. PMID: 32299789.

and into early adulthood (up to age 30).[1164,1165,1166] NCANDA will also seek to understand the impact of the COVID-19 pandemic on alcohol abuse among study participants.

NIAAA encourages research to increase the understanding of the effects of alcohol use on the brain and body of older adults, such as the link between advanced age and the risk for alcohol-induced brain damage and cognitive decline. In FY 2020, NIAAA partnered with NIA to expand research on the neurobiological mechanisms that underlie the influence of alcohol on the onset and progression of AD and related dementias.[1167] Research topics include a longitudinal study of the effects of alcohol on brain function in adults over age 50, as well as preclinical studies investigating potential molecular and cellular mechanisms through which alcohol may influence AD.

The co-use of alcohol and other substances during pregnancy poses a significant public health concern. A clinical study supported through a collaboration between NIAAA, NICHD, and NIDCD showed that combined exposures to alcohol and tobacco past the first trimester of pregnancy increased the risk of sudden infant death syndrome almost 12-fold, more than double the risk of either tobacco or alcohol alone.[1168] The findings underscore the need for increased public awareness of the dangers of prenatal exposure to alcohol and other substances, and for additional research to inform prevention and treatment.

NIAAA supports the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), a multidisciplinary consortium of domestic and international researchers that focuses on improving the diagnosis, prevention, and treatment of FASD. In 2020, NIAAA-funded researchers reported the results of a study aimed to initiate systematic development and evaluation of a mobile health intervention for caregivers raising children with FASD.[1169] In 2021, NIAAA renewed funding for the CIFASD consortium to continue to build on its research progress and train a new generation of FASD researchers.[1170]

Tobacco Use[1171]

NIDA's annual Monitoring the Future survey assesses substance use behaviors and attitudes in adolescents and young adults. In 2019, Monitoring the Future data showed steep increases in the use of vaping devices both for nicotine and for marijuana among teenagers.[1172] The survey also revealed that a

[1164] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-007.html
[1165] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-008.html
[1166] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-009.html
[1167] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-20-006.html
[1168] Elliott AJ, et al. *EClinicalMedicine*. 2020;19:100247. PMID: 32140668.
[1169] Petrenko CL, et al. *JMIR mHealth and uHealth*. 2020;8(4):e14721. PMID: 32250274.
[1170] https://grants.nih.gov/grants/guide/rfa-files/RFA-AA-21-010.html
[1171] The term "tobacco" here refers to "commercial tobacco," or products that are made and sold by tobacco companies, not including "traditional tobacco" used by Indigenous groups for religious or ceremonial purposes.
[1172] https://archives.nida.nih.gov/news-events/news-releases/2019/12/vaping-of-marijuana-on-the-rise-among-teens

large proportion of teens vaped because they liked the taste. In 2020, the FDA finalized an enforcement policy on flavored cartridge-based vaping and e-cigarette products.[1173]

The emergence and rapid uptake of e-cigarettes and vaping have changed the way that nicotine and cannabis are being consumed, resulting in new health risks. The Population Assessment of Tobacco and Health (PATH) Study, a collaboration between NIDA, TRSP, and the FDA's Center for Tobacco Products, assesses population-level patterns of tobacco and nicotine use to inform the development of interventions for preventing and treating substance misuse.[1174] In 2020, PATH Study data helped to inform an FDA policy that prioritized enforcement against certain unauthorized flavored cartridge-based products that appeal to youth.

HIV and Substance Misuse

A significant portion of NIDA's research portfolio funds science at the intersection of substance use and HIV and AIDS, due to the intertwined nature of these two health conditions. In 2021, NIDA's AIDS Research Program was renamed the HIV Research Program to better characterize NIDA's scientific investment and to help combat the stigma still attached to HIV and AIDS.[1175] NIDA's portfolio of HIV-related research ranges from basic science to implementation research. The program includes research on increased vulnerability of the immune system brought on by chronic exposure to addictive substances, the risks of HIV acquisition associated with injection drug use, and prevention of high-risk sexual behaviors associated with substance misuse.

To identify best practices for prevention, NIDA funds research that explores the complex intersection of HIV/AIDS and substance use disorders, including the risks associated with injection drug use. Current antiretroviral therapies (ART) to treat HIV suppress the replication of the virus to undetectable levels. While ART can enable people with HIV to achieve normal, healthy lifespans, ART cannot cure HIV since the dormant virus hides from detection in viral reservoirs in the body of most people with HIV, despite taking treatment regularly. NIDA-supported researchers investigated a subset of people with HIV who are able to maintain suppressed viral loads for years without ART. In 2020, the researchers reported that this group of people had HIV integrated into their immune cell genomes in specific locations where the DNA was turned off or silenced, so HIV replication could not occur.[1176] Additional experiments suggested that the immune systems of some people among this group may eliminate host cells in which HIV is integrated into the genome in locations that stimulate virus production. Sustained, drug-free control of HIV replication is naturally achieved in less than 0.5 percent of infected individuals despite the presence of a replication-competent viral reservoir.[1177] Further research is needed to determine exactly how these individuals' immune systems identify and eliminate cells harboring dormant HIV, and how the immune

[1173] https://www.fda.gov/tobacco-products/ctp-newsroom/enforcement-actions-against-illegally-marketed-tobacco-products
[1174] www.nida.nih.gov/research/nida-research-programs-activities/population-assessment-tobacco-health-path-study
[1175] https://nida.nih.gov/about-nida/noras-blog/2021/09/nidas-hiv-research-program-longstanding-institute-priority-continues-under-new-name
[1176] Jiang C, et al. *Nature*. 2020;585(7824):261-267. PMID: 32848246.
[1177] Sáez-Cirión A and Pancino G. *Immunol Rev.* 2013 Jul;254(1):281-94. PMID: 23772626.

systems of others might be stimulated to do the same. The paper in which the study results were reported was selected as a runner up for *Science* magazine's Breakthrough of the Year in 2020.[1178]

Information Dissemination, Workshops, and Events

In 2020, NIDA and NIAAA celebrated the 10th year of the National Drug and Alcohol Facts Week (NDAFW).[1179] This annual event is organized by NIDA and NIAAA and provides a forum for teens to interact with scientific experts and receive necessary information to make better choices about their health and substance use. Since it first started in 2010, NDAFW has grown in size and scope. In 2019, schools, community groups, and prevention organizations held or organized nearly 2,000 events in all 50 U.S. states and in 20 countries. In 2020, events pivoted from in-person to mostly virtual as COVID-19 shut down schools across the U.S., but the forum had over 2,700 events worldwide and an over 800 percent increase in listenership. In 2021, there were approximately 500 virtual events that included new content and an article entitled *Teens' ten Frequently Asked Questions About Drugs and Health*.

Figure 29: National Drug and Alcohol Facts Week. Credit: NIDA

Workplace stress, fatigue, and addiction are associated with increased occupational injury and illness.[1180] Negative health effects range from high blood pressure, obesity, burnout, depression, PTSD, substance misuse, addiction, and death. NIEHS Worker Training Program awardees developed safety and health training for workers engaged in activities related to hazardous materials and waste generation, removal, containment, transportation, and emergency response. In 2019, NIEHS held a workshop as a follow-up to the fall 2018 NIEHS Worker Training Program technical workshop focused on opioid-related hazards in the

[1178] https://vis.sciencemag.org/breakthrough2020/#/finalists/how-elite-controllers-keep-hiv-at-bay
[1179] https://archives.nida.nih.gov/news-events/noras-blog/2020/03/national-drug-alcohol-facts-week-celebrates-its-10th-year
[1180] Salvagioni DAJ, et al. *PLOS ONE*. 2017;12(10):e0185781. PMID: 28977041.

workplace.[1181] The 2019 workshop focused on interventions, training initiatives, and best practices in the U.S. and internationally. Awardees also provided program updates, exchanged information regarding training, and discussed how work-related stress may contribute to substance use and addiction.

Deaths from drug overdose continue to contribute to mortality in the U.S., with nearly 107,000 overdose deaths in 2021.[1182] In 2019, with support from the NIH HEAL Initiative, NCATS co-hosted a two-day symposium with NIDA and NINDS to address the opioid crisis through science.[1183] The symposium brought together pain and addiction researchers who discussed key challenges and opportunities in developing effective non-addictive treatments. During the last session of the symposium, NCATS, NIDA, and NINDS staff highlighted opportunities for funding and research collaboration, as well as resources to help researchers take those next steps. NCATS' Assay Guidance Manual was highlighted as a free online guide for developing rigorous assays for drug discovery.[1184] NCATS is currently compiling new tools, methodologies, and technologies that will be included in the next update of the guidance manual.

Resources

Screening, brief intervention, and referral to treatment by clinicians in general medical settings can promote significant reductions in alcohol and tobacco use, and there is also increasing literature suggesting potential reductions in illegal and nonmedical prescription drug use.[1185] NIDA's physicians' outreach initiative, NIDAMED, includes a suite of science-based resources about screening, addressing, and treating addiction. The NIDAMED initiative is aimed at engaging and educating clinicians in training and practice in the latest science relating to drug use and addiction. NIDAMED facilitated a national partnership between the NIH and the American Dental Association on ways to enhance and support dentistry's role in preventing opioid misuse. As part of NIDA's continuing support of NIDAMED, the Science to Medicine initiative was launched to help engage the clinician community in integrating cutting-edge research into their practice. NIDAMED also developed new resources in collaboration with emergency department specialists.[1186,1187] NIDAMED enables physicians to be the first line of defense against substance misuse and addiction and to increase awareness of the likely impact of substance misuse on a patient's overall health.

[1181] https://www.niehs.nih.gov/news/events/pastmtg/hazmat/2019/Spring_meeting/

[1182] Spencer MR, et al. Drug overdose deaths in the United States, 2001–2021. NCHS Data Brief, no 457, 2022. https://www.cdc.gov/nchs/products/databriefs/db457.htm

[1183] https://ncats.nih.gov/pubs/features/heal-symposium

[1184] https://ncats.nih.gov/expertise/preclinical/agm

[1185] Substance Abuse and Mental Health Services Administration. *Systems-Level Implementation of Screening, Brief Intervention, and Referral to Treatment.* 2013. https://store.samhsa.gov/product/TAP-33-Systems-Level-Implementation-of-Screening-Brief-Intervention-and-Referral-to-Treatment-SBIRT/SMA13-4741

[1186] D'Onofrio G, et al. *JAMA*. 2015;313(16):1636. PMID: 25919527.

[1187] https://nida.nih.gov/nidamed-medical-health-professionals/discipline-specific-resources/emergency-physicians-first-responders/initiating-buprenorphine-treatment-in-emergency-department

The NIAAA Alcohol Treatment Navigator® is a comprehensive, yet easy-to-use online tool to help individuals and their loved ones find professionally led, evidence-based treatment for alcohol AUD.[1188, 1189] In 2019, NIAAA created a new portal titled Make Better Referrals with the NIAAA Treatment Navigator to help health care professionals use the Treatment Navigator to connect patients to the full range of professional alcohol treatment providers offering evidence-based AUD treatments. In response to the COVID-19 pandemic, the Treatment Navigator and portal were updated with information about telehealth and online treatment options that are likely to play a larger role in alcohol prevention, treatment, and recovery. Grounded in decades of clinical and health services research, this one-of-a kind resource outlines the features of evidence-based AUD treatment, describes the varied routes to recovery, and guides individuals through a step-by-step process for finding evidence-based treatment.

The National Drug Early Warning System (NDEWS) is a surveillance network that monitors emerging trends related to illicit drug use in the U.S., so that rapid, informed, and effective public health responses can be developed and implemented when and where they are needed.[1190] In 2020, NIDA funded the second iteration of NDEWS that incorporates real-time surveillance to detect early signals of potential drug epidemics. The new system implements an expanded Early Warning Network that includes 18 sentinel sites utilizing novel surveillance methods. Ongoing data collection will provide an integrated and comprehensive characterization of drug use and availability by synthesizing traditional, indirect sources with new, direct sources of data, as well as on-the-ground epidemiologic investigations within high-priority areas of concern.

Transplantation

Since the first successful kidney transplant was performed between identical twins in 1954, transplantation has become the treatment of choice for end-stage organ failure. In the U.S., the most commonly transplanted organs are the kidney, liver, heart, lungs, pancreas, and intestines. On any given day, approximately 64,000 people are on the active waiting list for organs,[1191] but only around 14,000 deceased organ donors are available each year, with each providing on average 3.5 organs.[1192] Despite tremendous progress, however, major barriers still remain to the overall success of transplantation, which include immunological incompatibility between donor and recipient, acute rejection, chronic graft dysfunction, and complications from requisite long-term use of immunosuppressive drugs. NIH supports basic and clinical research that focuses on the immunologic processes underlying transplant rejection and acceptance, ways to reduce or eliminate the need for immunosuppressive drugs, procedures to increase organ storage time, and the development of new, less toxic antirejection therapies.

There are many more people in need of organ transplantations than available organs for transplanting-a shortage that is even more critical in specific populations. For example, people living with HIV have a growing prevalence of end-stage kidney disease and are nearly three times more likely to die while on

[1188] www.niaaa.nih.gov/news-events/news-releases/niaaa-alcohol-treatment-navigator-points-way-quality-treatment
[1189] https://alcoholtreatment.niaaa.nih.gov/
[1190] https://ndews.org/
[1191] OPTN data: UNOS Weekly Fact Sheet (Sept 24, 2021).
[1192] https://www.cdc.gov/transplantsafety/overview/key-facts.html

kidney dialysis than people without HIV. Kidney transplantation extends the lives of people with HIV and end-stage kidney disease, but these individuals face a shortage of donors and limited access to donor kidneys. NIAID-funded researchers showed that kidney transplantation from deceased donors with HIV to people living with both HIV and end-stage kidney disease is feasible and safe. The study results demonstrate that the pool of available kidneys for people with HIV can be expanded by including donors with HIV, making more kidneys available for those who are awaiting a transplant.[1193,1194]

Recognizing that lung transplantation could be a cure for millions of patients with COPD and other advanced lung diseases, NHLBI is committed to advancing this approach. While organ transplant outcomes have steadily improved in recent years, the mortality rate for lung transplants remains nearly twice as high as compared to heart, liver, and kidney transplants. To accelerate advances in lung transplantation, NHLBI is establishing a multi-site Lung Transplant Consortium that will harmonize clinical studies across lung transplant centers. Research data and biospecimens collected across these lung transplant centers will serve as a critical first step in facilitating future clinical trials that aim to improve donor lung utilization and short- and long-term outcomes for transplant recipients.[1195]

Figure 30: Scientists triple storage time of human donor livers. Credit: Massachusetts General Hospital

A large barrier to the overall success of organ transplantation is safe and effective storage of organs between the time they are collected from donors to the time they are transplanted into recipients, who could be located thousands of miles away. New research supported by NIBIB and NIDDK has led to the tripling of the amount of time human livers can potentially be stored before transplantation, from an average of 9 hours to 27 hours. Previous NIH-funded studies extended the amount of time rat livers can be stored prior to transplantation, but translating the procedure to human livers, which are 200-times larger, did not work as well. Scientists modified the protocol to account for the larger size of human livers,

[1193] https://www.niaid.nih.gov/news-events/kidney-transplantation-between-people-hiv-safe-nih-study-finds
[1194] Durand CM, et al. *Am J Transplant* 2021;21(5):1754-1764. PMID: 32701209.
[1195] https://grants.nih.gov/grants/guide/notice-files/NOT-HL-20-752.html

and initial results suggest the new procedure is successful, as traditional standards of assessing liver viability indicate that this process will not negatively affect the organ. Final confirmation will come in a future clinical trial where the scientists will implant a liver preserved using this new method into a human subject.[1196]

There are many more people in need of heart and heart tissue transplantations than available organs and tissues for transplanting. Although still a long way off, scientists are making great strides towards being able to grow tissues and organs for transplantation in the lab using 3D printing technology. In research partially funded by a New Innovator Award from the NIH Common Fund,[1197] scientists were able to 3D print a working heart valve and other components of a human heart. These proof-of-concept experiments demonstrated improvements the researchers made in fine manipulation of the biomolecules of the extracellular matrix (the scaffold that supports all our tissues and organs). Of particular importance was the researchers' ability to 3D print collagen, creating a minute and complex biological structure that could support heart cells and behave like heart tissues. The 3D printed structures even showed synchronized contraction like the beating of a heart.[1198,1199] But there are still many challenges to overcome on the long road ahead; a major one being the need to generate and incorporate billions of human cells that would be needed to produce a transplantable human heart or other organ.

Urologic and Gynecologic Diseases and Conditions

Diseases and conditions affecting the bladder and associated structures of the lower urinary tract affect people of all ages, result in significant health care expenditures, and may lead to substantial disability and impaired quality of life. Gynecologic conditions such as uterine fibroids, adenomyosis, endometriosis (a painful condition where tissue similar to the lining of the uterus grows in other places in the body), ovarian cysts, and menstrual disorders account for a significant amount of health burden among women across the U.S. Spearheaded by NICHD and NIDDK, NIH supports all areas of research to help improve the health of those affected by urologic and gynecologic diseases and conditions, conducting investigations into the epidemiology, natural history, etiology, basic mechanisms, prevention, diagnosis, and treatment of these diseases.

Understanding Prevalence, Risk Factors, and Underlying Biology

Fibroids, or leiomyomas, are noncancerous tumors that grow in or on the wall of the uterus, can cause pain and abnormal uterine bleeding or make it difficult for a woman to get pregnant and maintain a pregnancy. Although they can be treated, fibroids lead to about 300,000 hysterectomies in the U.S. each year. Scientists found that the 2-Methoxyestradiol (2-ME) compound hinders the reproduction of certain tumor cells and halts the development of new blood vessels that tumors need to survive. However, studies in animals and humans have found that 2-ME is rapidly broken down in the body before it can reach concentrations high enough to affect tumors. To deliver 2-ME directly to fibroids, NICHD-supported researchers encapsulated the drug in liposomes (nano-sized spheres made of the same molecules found

[1196] https://www.nibib.nih.gov/news-events/newsroom/scientists-triple-storage-time-human-donor-livers
[1197] https://commonfund.nih.gov/newinnovator
[1198] https://directorsblog.nih.gov/2019/10/10/3d-printing-a-human-heart-valve/
[1199] Lee A, et al. *Science* 2019 Aug 2;365(6452):482-487. PMID: 31371612.

in cell membranes) and injected the 2-ME-containing liposomes into a strain of immune-deficient mice that had received transplants of human fibroids. After 28 days, tumors of the treated mice were about 30 percent smaller than those in untreated animals. Treated tumors also had fewer multiplying cells and a higher proportion of dead cells, indicating that the drug was reaching its target. These findings suggest that 2-ME could potentially provide a treatment for women with fibroids.[1200]

NICHD conducts and supports basic, translational, and clinical research, and research training programs related to gynecologic health in women and adolescent girls. Their portfolio emphasizes studies of the menstrual cycle, uterine fibroids, endometriosis, polycystic ovary syndrome (a set of symptoms related to hormonal imbalance, resulting in irregular periods, excessive hair growth, acne, and infertility), and pelvic floor disorders, as well as studies of the mechanisms underlying chronic pelvic pain and vulvodynia. Recently, NICHD sought to spur additional research in key areas, such as technologies to advance precision medicine for reproductive health and infertility, the role of stem cells in the pathogenesis and treatment of gynecologic disorders, and noninvasive diagnostics to improve gynecological health. In response to the COVID-19 pandemic, NICHD supported research on the effects of COVID-19 vaccination on menstruation. Researchers found that COVID-19 vaccines may slightly lengthen the menstrual cycle, but these effects are temporary and not clinically significant.[1201,1202,1203,1204,1205, 1206,1207]

Urinary tract infections (UTIs) are often caused by uropathogenic *E. coli* (UPEC), a group of strains known for causing UTIs, and the threat of increasing bacterial antibiotic resistance is driving research to identify new therapeutic approaches. NIDDK-supported researchers found that in mice, rather than an antibody response to ridding the body of UPEC, the mouse immune response is typically biased toward aiding repair of the bladder lining. Thus, multiple rounds of UPEC infection led to a thickening of the bladder lining that ultimately reduced mouse bladder capacity. Repair of the bladder lining is critical for protecting underlying cells from noxious waste molecules present in urine. However, the high bias toward repair and consequent inhibition of a robust companion antibody response could be contributing not only to recurrent infection but also to bladder dysfunction, such as urinary urgency or incontinence.[1208] If these results are confirmed in humans, it could lead to changes in how UTIs are treated.

Historically, studies of people with urologic problems have often involved artificially filling the bladder with liquid using a catheter while simultaneously visualizing brain activity using MRI. The NIDDK-supported Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network pioneered a more natural approach. Sixty-two healthy men and women were asked to drink about 12 ounces of water after first voiding their bladders; 40 minutes later, they underwent an MRI brain scan for ten minutes,

---

[1200] Borahay MA, et al. *Reprod Sci.* 2021 Jan;28(1):271-277. PMID: 32632769.
[1201] https://www.nichd.nih.gov/about/org/der/branches/ghdb
[1202] https://grants.nih.gov/grants/guide/notice-files/NOT-HD-21-035.html
[1203] https://www.nichd.nih.gov/newsroom/news/010622-COVID-19-vaccine-menstruation
[1204] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-20-010.html
[1205] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-20-007.html
[1206] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-21-020.html
[1207] Edelman A, et al. *Obstet Gynecol*. 2022 Apr 1;139(4):481-489. PMID: 34991109.
[1208] Wu J, et al. *Nat Immunol*. 2020 Jun;21(6):671-683. PMID: 32424366.

emptied their bladders into a urine collection container, and underwent a second ten-minute scan. The researchers found that activity in specific brain regions and networks associated with bladder filling and voiding, from sensory recognition to physical response, not only was detectable, but also correlated with perceived urinary urgency and with void volumes. This study provides proof that a more natural bladder filling method that avoids invasive catheterization is effective for studying brain activities important to urologic function and correlating them with people's symptom experiences. If confirmed, this new approach potentially makes future research easier on participants and enables inclusion of larger and more diverse groups of people.[1209]

Improving Treatment and Prevention

Pediatric and adolescent gynecology is a relatively new subspecialty within the field of obstetrics and gynecology and encompasses gynecologic care from the fetal period into adulthood. This includes congenital anomalies of the reproductive tract (including disorders of sex development), oncology, fertility, medical/endocrine conditions, and structural gynecologic conditions. NICHD intramural researchers are focusing on fertility preservation, which includes procedures to maintain a person's ability to have children. These may give patients with cancer or other rare disorders that affect fertility the opportunity to possibly have biological children in the future. NICHD intramural research priorities in this program also include childhood and adolescent beginnings of gynecologic conditions (e.g., endometriosis and polycystic ovary syndrome), rare gynecological conditions, and rare diseases with associated gynecologic conditions.[1210] Many of these rare diseases and have been insufficiently studied in the past.

In 2021, NICHD established the Centers to Advance Research in Endometriosis program, with the goal of improving prevention and treatment options for women with endometriosis. The scope of this program includes basic, translational, and clinical projects that will enhance our understanding of the etiology, pathophysiology, and progression of endometriosis and enable the development of more effective strategies for the diagnosis, management, and prevention of this disorder. Examples of funded projects under this initiative include leveraging single-cell technologies to determine immune mechanisms, determining environmental signatures of endometriosis, imaging and treatment of endometriosis in non-human primates, community engagement, and computational approaches to identify novel therapeutic candidates for treating endometriosis.[1211]

Lower urinary tract symptoms (LUTS) are associated with any type of lower urinary tract dysfunction or condition (e.g., urinary incontinence (UI), urinary tract infections), as well as those with as-yet unidentified cause. LUTS, which can include frequent or urgent urination, needing to get up multiple times at 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 chronic health problems in women, including obesity, diabetes, and depression. NIDDK is supporting many initiatives to better understand LUTS and develop more effective treatments and therapies.

[1209] Mawla I, et al. *Sci Rep*. 2020 Nov 16;10(1):19901. PMID: 33199816.
[1210] https://www.nichd.nih.gov/research/atNICHD/Investigators/gomez-lobo/research
[1211] https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-21-002.html

One initiative is the Lower Urinary Tract Dysfunction Research Network (LURN), established to better define clinical phenotypes, better describe the impact and diversity of symptoms, and develop new patient-centric tools for improved measurement of clinical symptoms, all with the goals of informing future clinical studies and improving patient care. In the second five-year funding cycle, LURN investigators will continue subtyping participants with LUTS with the expectation that clinically useful patient subtypes will be identified. Research efforts will include both continued analysis of data and the development of additional, new, and novel collaborative studies to further improve our understanding of lower urinary tract dysfunction. One example of LURN findings comes from a study of 510 female participants, that found that found that although the majority reported having UI, increasing UI severity rather than the presence or type of UI was associated with increased depression, anxiety, and stress. Another example comes from a study in this same group that found that women with UI reported significantly worse constipation, diarrhea, fecal incontinence, and sexual function compared to women without UI.[1212,1213]

A second initiative, the multi-center, multidisciplinary Prevention of Lower Urinary track Symptoms (PLUS) Research Consortium, is pursuing qualitative and quantitative research studies necessary to establish the scientific basis for future prevention-intervention research targeting LUTS in women and girls. Bladder health measurement is challenged by a lack of awareness of normal function, use of self-management strategies to manage symptoms, and a common tendency to overlook infrequent LUTS. PLUS scientists have developed and published a novel, multi-faceted research definition of bladder health that can inform approaches for more accurate evaluation of bladder health. PLUS scientists also conducted a review and meta-analysis of nearly 30 years of published studies and found a profound gap in the ability to evaluate LUTS by occupation types, indicating that future studies should characterize voiding frequency and toilet access in a consistent manner by occupation and explore its relation to LUTS development.[1214]

People with UCPPS (interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome) experience pelvic pain and urologic symptoms, such as increased urinary frequency and urgency. When symptoms worsen, it is called a flare. An NIDDK-supported study lasting nearly a year found that about 75 percent of the 400 participants reported experiencing at least one flare, and the duration of flares varied between as short as one day or as long as 150 days. The risk of worse and/or longer flares was greater in women, in individuals who had more severe UCPPS symptoms overall when not having a flare, and in those with bladder pain associated with filling and/or urgency to urinate (bladder hypersensitivity). Finally, people with UCPPS commonly had co-occurring chronic pain conditions, such as irritable bowel syndrome, which were also risk factors for worse flares.[1215]

Overactive bladder is a condition that affects millions of people and causes a frequent need to urinate, incontinence, and increase in bladder voiding. The NIH Common Fund's Stimulating Peripheral Activity to Relieve Conditions program supported development of a miniature implanted device that can sense and

[1212] https://nih-lurn.org/
[1213] https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-18-510.html
[1214] https://plusconsortium.umn.edu/
[1215] Sutcliffe S, et al. *BJU Int*. 2019 Sep;124(3):522-531. PMID: 31012513.

control bladder function, and successfully tested it in an animal model. This approach used a stretch sensor that measured changes in bladder expansion over time coupled with a technique called optogenetics, where genetically modified nerve cells can be activated or inhibited using light. When the sensor detected signs of overactive bladder, it wirelessly transmitted a signal causing light-drive inhibition of nerves affecting bladder emptying, thus preventing abnormal frequency of urination.[1216]

About 1.5 million U.S. women of reproductive age are estimated to suffer from infertility.[1217] Many more have difficulty getting pregnant. Menstrual cycles are an indicator of a woman's general health. Menstrual cycle changes may predict difficulties in getting pregnant. Menstrual cycles are controlled by a complex cascade of signals controlled by the brain and the hypothalamic-pituitary-ovarian axis. A NIEHS-supported study will investigate vitamin D's influence on the hypothalamic-pituitary-ovarian axis through careful evaluation of hormonal, ovulatory, and overall menstrual cycle changes that occur with vitamin D treatment. Depending on study results, treating patients with vitamin D supplements may be a low-cost intervention that improves menstrual cycle function and fertility.[1218]

Autoimmune Diseases

A healthy immune system defends the body against disease and infection, but if the immune system malfunctions, it can mistakenly attack healthy cells, tissues, and organs. This condition is identified as autoimmune disease. These attacks can affect any part of the body, weakening bodily function, and can be life threatening.

There are more than 80 known autoimmune diseases, which affect more than 24 million people in the U.S. An additional eight million people have auto-antibodies, blood molecules that indicate a person's chance of developing autoimmune disease. Autoimmune diseases are currently affecting more people, for reasons unknown, which warrants additional research to better understand the causes of autoimmune diseases and to help develop treatments and cures.

Some autoimmune diseases are well known, such as type 1 diabetes, multiple sclerosis (MS), systemic lupus erythematosus (SLE or lupus), IBD, and RA, while others are rare and difficult to diagnose. More information about NIH research on diabetes, MS, and IBD is available in other sections of this chapter. With unusual autoimmune diseases, patients may suffer years before getting a proper diagnosis. Most of these diseases have no cure, and some require lifelong treatment to ease symptoms. Although the causes of many autoimmune diseases remain unknown, a person's genes in combination with infections and other environmental exposures are likely to play a significant role in disease development.

[1216] Mickle AD, et al. *Nature.* 2019 Jan;565(7739):361-365. Epub 2019 Jan 2. PMID: 30602791.

[1217] Chandra A, et al. Infertility and Impaired Fecundity in the United States, 1982–2010: Data from the National Survey of Family Growth. *National Health Statistics Reports*. 2013. https://www.cdc.gov/nchs/data/nhsr/nhsr067.pdf.

[1218] https://clinicaltrials.gov/ct2/show/NCT05050916?term=National+Institute+of+Environmental+Health+Sciences&recrs=adf&draw=2&rank=3

Summary of NIH Activities

NIH is committed to advancing the Nation's understanding of autoimmune diseases: what causes them, how they develop, and how that knowledge can be applied to improve the health and quality of life for patients affected by autoimmune diseases. Much work has been done, and much work still remains.

NIH supports research on the underlying genetics and immune responses, risk factors, screening, diagnosis, treatment, and management of autoimmune diseases, as well as on identifying emerging autoimmune diseases. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH ICOs (including NCCIH, NCI, NHGRI, NHLBI, NIA, NIAID, NIAMS, NICHD, NIEHS, and NINDS) conduct and support autoimmune disease research. For example, NIAMS, in partnership with NIAID, contributes to the AMP in two disease areas: RA and lupus.[1219] The AMP RA/lupus research network focuses on immune and tissue cells from organs affected by the diseases, including cells from the joints of individuals with RA and from the kidneys and skin of people with lupus. The network is adapting new technologies to allow those cells to be analyzed individually using high-throughput approaches. The program is making its data available to the broader research community to foster additional research on autoimmune diseases and enhance the return on investment in the program. NIH funding for autoimmune disease research was $988 million in FY 2019, $1,083 million in FY 2020, and $1,021 million in FY 2021.[1220]

Understanding the Biology

Although researchers have made considerable progress in understanding how the immune system causes organ, tissue, and cell injury in autoimmune diseases, much remains to be learned. NIH continues to support a broad range of basic, preclinical, and clinical research in autoimmune diseases, so that research findings can enhance our understanding of the causes of these diseases, the genetic factors that make people susceptible to them, and the regulatory mechanisms that control the production of self-destructive antibodies.

Immune Cells and Inflammation

Women develop certain autoimmune diseases more often than men, something which is not completely understood. Therefore, further study is essential to better understand how sex influences the differences in the immune system and specific immune cells.

Neutrophils are part of the innate immune system, the arm of the immune system that is fast-acting and non-specific, and act as the sentinels of the body, oftentimes arriving first on the scene of any infection or threat. Recent work showed that female neutrophils have striking upregulation of genes that are stimulated by type I interferon (IFN), suggesting an enhanced response to this group of antiviral cytokines.[1221] Researchers also identified differences in the cellular metabolism of female and male neutrophils that appeared to be driven by sex hormones, such as estradiol or estrogen. The differences observed in neutrophil function between adult males and females were not observed in prepubertal boys and girls. In addition, neutrophils from patients with Klinefelter's syndrome (men who have two copies of

[1219] www.niams.nih.gov/grants-funding/funded-research/accelerating-medicines/RA-SLE
[1220] https://report.nih.gov/funding/categorical-spending#/
[1221] Gupta S, et al. *Proc Natl Acad Sci U S A* 2020 Jul 14;117(28):16481-16491. PMID: 32601182.

the X chromosome and one Y rather than one of each) did not differ in their type I IFN response when compared with males without Klinefelter's, further supporting the role of sex hormones rather than the X chromosome in driving this difference.

Another type of innate immune cell, the macrophage, is particularly good at cleaning up infections, by taking in and digesting either a pathogen itself or other pathogen-infected cells. It typically responds to known "eat me" or "don't eat me" signals. A team of researchers delineated a code that macrophages use to signal and respond to a pathogen threat.[1222] The researchers have identified not just a lone distress signal, or single word, but rather a vocabulary of six words. Their studies show that macrophages use these words at different times to launch an appropriate immune response.[1223] They also have evidence that autoimmune conditions can arise when immune cells misuse certain words in this vocabulary. While previous studies have proposed that immune cells use a language to communicate with one another, this is the first study to identify words in that language, and to show what can happen when those words are misused. The next step is to figure out the precise definitions and interpretations of the words and, ultimately, how their misuse may be corrected to treat immunological diseases.

The counterpart to the innate immune system is the adaptive immune system, which is slower and much more specific; the actions of the innate immune system activate cells of the adaptive immune system. T cells, named for their origins in the thymus, are a part of the adaptive immune system and are trained to recognize specific types of pathogens or abnormal cells.

NIH-funded scientists studying autoimmune diseases identified an unexpected protective function for a type of T cell normally known to destroy cancerous or infected cells. In a mouse model of MS, this immune cell helped reduce the severity of the disease and could one day become a useful therapeutic target in treating autoimmune diseases in humans.[1224]

Inflammation is a normal part of the body's defense to injury or infection and can be beneficial. However, inflammation is damaging when it occurs in healthy tissues or lasts too long. Known as chronic inflammation, it may persist for months or years. Chronic inflammation is associated with many autoimmune diseases.

Using a mouse model of MS, researchers found that during the progressive phase of the disease, astrocytes (a type of cell in the brain that works to maintain a steady state) switched on metabolic pathways that activated a protein called the mitochondrial antiviral signaling (MAVS) protein.[1225] This led to activation of several proinflammatory genes, triggering inflammation in the brain and spinal cord.[1226] If the scientists gave the mice the drug miglustat before the onset of MS, they were able to suppress MAVS

[1222] https://directorsblog.nih.gov/2021/07/07/immune-macrophages-use-their-own-morse-code/
[1223] Cheng QJ, et al. *Science* 2021 Jun 18;372(6548):1349-1353. PMID: 34140389.
[1224] Saligrama N, et al. *Nature* 2019 Aug;572(7770):481-487. PMID: 31391585.
[1225] https://factor.niehs.nih.gov/2020/2/papers/dert/index.htm#a3
[1226] Chao CC, et al. *Cell* 2019 Dec 12;179(7):1483-1498.e22. PMID: 31813625.

activation and subsequent inflammation. The findings suggest a new role for MAVS in central nervous system (CNS) inflammation and a potential therapeutic target for MS.

Immune cells are not the only cells responsible for the persistent inflammation of RA, and cells of the joint tissue called fibroblasts also play a role. Fibroblasts are activated by elevated levels of inflammatory molecules, including tumor necrosis factor (TNF) and interleukin 17A (IL-17A), which drive inflammation in RA. Using cutting-edge technologies to characterize how gene expression changes in fibroblasts in response to TNF and IL-17A, researchers found that IL-17A needs TNF in order to induce an inflammatory response in fibroblasts.[1227] Researchers identified two critical molecules in fibroblasts that mediate the inflammatory response to TNF and IL-17A, as well as the mediators necessary for recruiting more immune cells to drive the inflammation. This knowledge may enable researchers to identify approaches to target these molecules and the mediators, in order to reduce the inflammation experienced by patients with RA.

Although RA pain has commonly been thought to result from inflammation, it often persists even after optimal control of inflammation with currently available therapies, indicating the involvement of other non-inflammatory mechanisms. Researchers identified how immune complexes (molecules formed from an antibody binding to multiple targets) trigger arthritis pain via an inflammation-independent mechanism, at least in part, through direct activation of receptors on nerve cells.[1228] These findings provide a new direction for therapeutic strategies to treat arthritis pain and imply that specific nerve receptors may be a potential target.

Glucocorticoids are among the most commonly used drugs in rheumatology due to their anti-inflammatory effects. When glucocorticoids are given, a type of innate immune cells called eosinophils disappear from the blood, but it is unclear where they go or why. Combining genomic studies in humans and live tracking of eosinophils in a rhesus macaque model, investigators discovered that glucocorticoids drive eosinophils to the bone marrow and that the mechanism of this migration involves the induction of a specific receptor on the surface of eosinophils.[1229] More research is needed to better understand the molecular mechanisms by which glucocorticoids affect specific immune cell types, which may pave the way for more targeted therapies that can mimic the good effects of glucocorticoids in specific disease states with fewer of the negative side effects.

Drugs are not the only way to control inflammation. Ultraviolet phototherapy can also be used. Using a mouse model susceptible to developing lupus, scientists recently discovered that ultraviolet phototherapy activates a cellular process that cleans up dying cells in a manner that does not inappropriately trigger the immune system.[1230] These findings give insights into autoimmune and inflammatory disorders and present new opportunities for treatment.

[1227] Slowikowski K, et al. *Proc Natl Acad Sci U S A* 2020 Mar 10;117(10):5532-5541. PMID: 32079724.
[1228] Wang L, et al. *J Clin Invest* 2019 Jun 18;129(9):3754-3769. PMID: 31211699.
[1229] Hong SG, et al. *Blood* 2020 Dec 3;136(23):2667-2678. PMID: 32659786.
[1230] Sil P, et al. *J Allergy Clin Immunol* 2020 May;145(5):1389-1405. PMID: 31837371.

Risk Factors

There are 90 known lupus genetic variants that increase the risk of developing lupus in an additive fashion, so if an individual has two risk variants, then they have twice the likelihood of developing lupus, if they have four risk variants then four times, and so forth. Normally, analyzing cell genomes requires sifting through DNA sequence by sequence, however, NIH-funded investigators were able to develop a variation of a genetic screening tool that can analyze thousands of DNA sequences simultaneously.[1231] Using this tool, researchers were able to provide the first report of a direct genome-wide measurement of whether a particular DNA sequence is likely to cause a gene to be transcribed (into RNA) for the full set of known lupus genetic risk variants. It represents a tremendous acceleration of discovery and opens the door for additional related lupus research to explore the new clues revealed from the study. In addition, this faster screening tool will likely boost efforts to dissect the genetic mechanisms of many other complex human diseases.

Figure 31: Collage of DNA molecules and images highlighting locations of joint inflammation such as seen during lupus flares. Credit: iStock; collage developed by Alisa Machalek (NIAMS)

In May 2019, at the fourth annual D.C. Lupus Consortium Meeting, NIH recognized the patients, providers, researchers, and advocates who have supported lupus research at NIH over the last 25 years. The meeting highlighted the progress in lupus clinical research made by NIH, specifically noting the success of the lupus natural history protocol.[1232] The event featured testimonials from research participants, updates on current lupus studies, and discussions of future topics to explore.

[1231] Lu X, et al. *Nat Commun* 2021 Mar 12;12(1):1611. PMID: 33712590.
[1232] archive.niams.nih.gov/newsroom/announcements/niams-celebrates-lupus-research-progress-fourth-annual-dc-lupus-consortium

New and Complementary Treatments

The complexity of autoimmune diseases makes them difficult to treat. Most current therapies involve broadly suppressing the immune system. These approaches can control some symptoms but come with serious side effects. To develop more targeted treatments for autoimmune diseases, scientists need a better understanding of the genes that help drive them.

One of the most promising areas of research in recent years has been gene editing, including CRISPR/Cas9, which can be used to fix misspellings in genes to treat or even cure many conditions. CRISPR is a highly precise gene-editing system that uses guide RNA molecules to direct a scissor-like Cas9 enzyme to just the right spot in the genome to cut out or correct disease-causing misspellings.

Researchers used CRISPR genome-editing technology to engineer "smart" cells that can sense changing levels of the inflammatory molecule interleukin-1 (IL-1) and produce therapeutic levels of its complementary anti-inflammatory molecule, interleukin-1 receptor antagonist (IL-1Ra).[1233] These smart cells were then implanted under the skin of mice with RA. The cells were able to live for up to five weeks and during this time successfully mitigated the inflammation, pain, and bone erosion associated with this disease model. This interdisciplinary research represents a new frontier in cell-based therapy, bridging various cutting-edge technologies to create a platform for novel drug discovery. Further studies in this direction could shed light on the treatment of diseases associated with a specific gene and/or pathway, and possibly even the treatment of comorbidities associated with autoimmune diseases.

Due to the inherently difficult nature of understanding and treating immune diseases, research is focused on understanding the role of less traditional or complementary therapies. Acupuncture is a technique in which practitioners stimulate specific points on the body, most often by inserting thin needles through the skin. It is one of the practices used in traditional Chinese medicine. Results from a number of studies suggest that acupuncture may help chronic types of pain, such as low-back pain, neck pain, and osteoarthritis or knee pain. It also may help reduce the frequency of tension headaches and prevent migraine headaches. However, researchers are only beginning to understand whether and how acupuncture can be helpful for various health conditions.

NIH-supported scientists published new data suggesting that acupuncture can reduce systemic inflammation, depending on the site, intensity, and timing of the treatment.[1234] In this study, researchers used electroacupuncture, a modern version of the traditional manual approach, which involves the insertion of ultra-thin needles just under the skin in various areas of the body. Instead of needles, electroacupuncture uses very thin electrodes inserted into the skin and into the connective tissue, offering better control of stimulation intensities. The researchers investigated organizational rules on how stimulation at specific body regions drives distinct autonomic nervous pathways, with a particular focus on prevention and treatment of systemic inflammation. These findings should help to improve acupuncture practice and could form a road map for optimizing stimulation parameters to improve efficacy and safety in using acupuncture as a therapeutic treatment. Before any therapeutic use, the

[1233] Choi YR, et al. *Sci Adv* 2021 Sep 3;7(36):eabj1414. PMID: 34516920.
[1234] Liu S, et al. *Neuron* 2020 Nov 11;108(3):436-450.e7. PMID: 32791039.

observations must be confirmed in further research, in animals as well as in humans, and the optimal parameters for acupuncture stimulation must be carefully defined.

Improving the Screening, Diagnosis, and Treatment of Autoimmune Disorders

With autoimmune diseases affecting more people, additional research is needed to better detect signs of autoimmune diseases and translate those signs into diagnoses and treatment regimens. Considering that many autoimmune diseases are chronic conditions, with patients experiencing periods of ups and downs, treatment regimens must also include plans for monitoring signs and symptoms and adjusting to improve quality of life.

Screening, Diagnosis, and Monitoring Disease

Although each autoimmune disease is unique, many share some of the same symptoms, and many symptoms of autoimmune diseases are the same for other types of health problems. Biomarkers are clinical signs or laboratory test results that correlate with the onset or progression of an autoimmune disease. Biomarkers hold great promise for earlier and more accurate autoimmune disease diagnosis, better prediction of disease flare-ups, and improved monitoring of disease progression and response to treatment.

Autoantibodies (immune system proteins that mistakenly target the body's own tissues) are a commonly used biomarker found in a wide range of autoimmune diseases, such as lupus and RA. Many people with low levels of autoantibodies in their blood have no obvious symptoms.[1235] Taken together, this makes it quite difficult for scientists to develop specific screening and diagnostic tools for autoimmune diseases.

In FY 2020, a team of NIH scientists reported a concerning rise in the prevalence of antinuclear antibodies (ANA), a type of autoantibody.[1236] This study is the first to evaluate ANA changes over time in a representative sampling of the U.S. population.[1237] The findings may indicate an increase in the number of people with autoimmune diseases.

RA symptoms occur as episodes of unpredictable worsening called flares, followed by improvement. Investigators who examined changes of gene expression in blood samples collected weekly from RA patients over four years found that B cells—immune cells that make antibodies—become activated about two weeks before a flare.[1238] Surprisingly, they also found that the number of an unexpected type of cells called preinflammatory mesenchymal (PRIME) cells, which are normally present in low levels in the blood, greatly increased in the days just prior to a flare and then disappeared during the flare itself. Importantly, the PRIME cells shared gene expression features with the fibroblasts found in the joint tissue of RA patients. Fibroblasts are a type of cell that contributes to the formation of connective tissue, and in RA are known to increase in numbers and become invasive, and are critical to the persistent inflammation of RA. These results suggest a model in which PRIME cells travel from the blood to the inflamed joint, where they mature into fibroblasts and become activated in the weeks prior to RA flares.

[1235] https://www.nih.gov/news-events/nih-research-matters/autoimmune-response-found-many-covid-19
[1236] https://factor.niehs.nih.gov/2020/5/papers/autoimmunity/index.htm
[1237] Dinse GE, et al. *Arthritis Rheumatol* 2020 Jun;72(6):1026-1035. PMID: 32266792.
[1238] Orange DE, et al. *N Engl J Med* 2020 Jul 16;383(3):218-228. PMID: 32668112.

These PRIME cells present a new biomarker that could be monitored to help predict RA flares, and direct treatment accordingly.

New and Repurposed Treatments

A properly functioning immune system is essential to a healthy life. Primary immune deficiency diseases (PIDDs) are rare genetic disorders that impair the immune system. Without a functional immune response, people with PIDDs may be subject to chronic, debilitating infections, such as Epstein-Barr virus (EBV), which can increase the risk of developing cancer. Some PIDDs can be fatal. PIDDs may be diagnosed in infancy, childhood, or adulthood, depending on disease severity. There are more than 200 different forms of PIDDs affecting approximately 500,000 people in the U.S. Severe combined immunodeficiency (SCID) is a group of PIDDs caused by mutations in different genes involved in the development and function of immune cells. Infants with SCID appear healthy at birth but are highly susceptible to severe infections.

Two separate clinical trials have shown that gene therapy can restore immune function in infants and children with SCID.[1239,1240] In one small clinical trial, eight infants with X-linked SCID received an experimental gene therapy co-developed by NIH scientists. The infants experienced substantial improvement in immune system function and were growing normally up to two years after treatment.[1241] In another clinical trial, 48 of 50 children with SCID due to adenosine deaminase deficiency (ADA-SCID) who received an experimental gene therapy retained their replenished immune system function two to three years later and did not require additional treatments for their condition.[1242] Both approaches appear to be safer and more effective than previously tested gene therapy strategies for SCID, presenting opportunities for vast improvements in quality of life for these patients.

Women with autoimmune diseases can safely have children, but there could be some risks for the mother or baby depending on the disease and how severe it is. For instance, pregnant women with lupus have a higher risk of preterm birth and stillbirth. For some women, symptoms tend to improve during pregnancy, while others find their symptoms tend to flare up. Also, some medicines used to treat autoimmune diseases might not be safe to use during pregnancy.

There are no MS drugs approved for use during pregnancy, and few studies have investigated their use in pregnant women. To learn more about MS drug safety in mothers and babies and current prescribing practice, NIH-supported scientists looked at a large database of patient data.[1243] They found that the use of MS drugs declined during pregnancy but increased after delivery, indicating that women were not taking MS drugs during pregnancy but restarted them afterwards. They also found that patients with MS had similar risks for poor birth outcomes and pregnancy complications, including pregnancy loss,

---

[1239] https://www.niaid.nih.gov/news-events/gene-therapy-restores-immunity-infants-rare-immunodeficiency-disease

[1240] https://www.niaid.nih.gov/news-events/gene-therapy-restores-immune-function-children-rare-immunodeficiency

[1241] Mamcarz E, et al. *N Engl J Med* 2019 Apr 18;380(16):1525-1534. PMID: 30995372.

[1242] Kohn DB, et al. *N Engl J Med* 2021 May 27;384(21):2002-2013. PMID: 33974366.

[1243] MacDonald SC, et al. *Pharmacoepidemiol Drug Saf* 2019 Apr;28(4):556-560. PMID: 30834654.

infection, cesarean delivery, preterm delivery, poor fetal growth, preeclampsia, and major congenital anomalies, regardless of whether they took MS drugs while pregnant. The risks for these outcomes and complications were similar for women with MS and women who did not have the disease. The scientists concluded that neither MS itself nor using MS drugs in early pregnancy appears to increase the risk for adverse pregnancy outcomes.

While asthma is a chronic lung disease caused by an immune response, it is not considered an autoimmune disease. Due to the immune system's role in asthma, several asthma drugs are being tested for use in autoimmune diseases.

Hypereosinophilic syndromes (HES) are a family of rare chronic immune disorders characterized by higher-than-normal numbers of eosinophils in the blood, tissues, or both. A drug approved to treat a severe form of asthma dramatically improved the health of people with HES in whom other treatments were ineffective or intolerable.[1244] This finding comes from a small, three-phase, clinical trial of benralizumab over a period of 48 weeks.[1245] Eosinophils were undetectable in the bone marrow of nine of the ten participants in the treatment group in the first phase, and in the tissue of all eight participants whose tissue was tested at the end of the second phase. A larger trial comparing benralizumab to placebo is needed to confirm these results and make further conclusions about its use for treating HES.

Another asthma drug is being repurposed for lupus. Lupus is characterized by the production of autoantibodies leading to an abnormal immune response. While prior research has shown that autoantibodies of the immunoglobulin G (IgG) subclass were the most pathogenic in lupus, more recent studies have revealed that immunoglobulin E (IgE) is also involved. In a pilot phase 1b clinical trial of patients with lupus, researchers evaluated the safety and tolerability of omalizumab, an FDA-approved drug for the treatment of asthma and hives that removes circulating IgE from the body and decreases immune responses to these autoantibodies.[1246] The investigators showed that omalizumab was well tolerated with no immediate or delayed allergic reaction when used as an add-on therapy. In addition, there was a modest improvement in lupus disease activity.

Severe drug hypersensitivities are life-threatening and can be extremely difficult to manage, posing significant clinical challenges. Adding to that challenge, multiple drug hypersensitivities are correlated with autoimmune diseases. Drug hypersensitivities can act more like a syndrome, where the immune system remains hyperactive even after use of the drug that caused the hypersensitivity is ended, leading either to chronic inflammation or to the subsequent onset of other autoimmune diseases. Researchers at the NIH Clinical Center used innovative technologies to understand gene expression profiles at the single-cell level in a patient with a life-threatening form of drug hypersensitivity syndrome for whom all conventional therapies had failed.[1247] They were able to identify a target for therapy and begin treatment, leading to reduced skin inflammation and normal levels of immune cells. In addition to having a huge

[1244] https://www.niaid.nih.gov/news-events/fda-approved-drug-effectively-treats-rare-chronic-immune-disorders
[1245] Kuang FL, et al. *N Engl J Med* 2019 Apr 4;380(14):1336-1346. PMID: 30943337.
[1246] Hasni S, et al. *Arthritis Rheumatol* 2019 Jul;71(7):1135-1140. PMID: 30597768.
[1247] Kim D, et al. *Nat Med* 2020 Feb;26(2):236-243. PMID: 31959990.

impact on the patient's life, this work represents a proof-of-concept study on how single-cell genomic technologies may broaden approaches taken for precision medicine.

Infectious Diseases and Biodefense

Infectious diseases pose a significant threat to human health, with many types of infections having far-reaching, global consequences—something NIH and the American public have been keenly aware of during FY 2019–2021 and the novel coronavirus disease 2019 (COVID-19) pandemic. The emergence of new pathogens, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus that causes COVID-19—and the re-emergence of certain microbes along with the growth of antimicrobial resistance, all require NIH and the biomedical and behavioral research community to be vigilant and ready to pivot to address public health needs. Our society is increasingly global, and efforts to combat infectious diseases and bolster biodefense require coordination that goes beyond geographic boundaries.

Of the top ten global health issues to track in 2021, as identified by WHO, nine out of ten were related to or influenced by COVID-19, with four being directly related to infectious diseases and biodefense: preparedness for pandemics and health emergencies, access to COVID-19 tests, medicines, and vaccines, efforts to tackle communicable (infectious and parasitic diseases and maternal, perinatal, and nutritional conditions) diseases, and combatting drug resistance.[1248] In 2020, CDC reports that three of the top ten leading causes of death in the U.S. are currently infectious diseases: COVID-19 (at third), chronic lower respiratory diseases (at sixth), and influenza and pneumonia (at ninth).[1249] In addition to naturally or accidently occurring infectious diseases, the deliberate release of pathogenic agents, such as anthrax or smallpox, could cause large-scale public health emergencies. NIH-supported research in infectious diseases and biodefense is essential to developing safe and effective medical countermeasures, including new prevention strategies, treatments, and diagnostics, to combat these growing threats.

Summary of NIH Activities

NIH continues to lead the way in generating the evidence needed to develop new and improved diagnostic tests, treatments, and vaccines for infectious diseases, as well as strategies for widespread implementation of these tactics. While many of NIH's resources were devoted to combating the COVID-19 pandemic, at the same time, NIH continued to make serious inroads into combating other infectious diseases and bolstering the Nation's biodefense. NIH's wide-ranging infectious disease portfolio includes research in HIV/AIDS, malaria, tuberculosis, viral hepatitis, and into emerging and re-emerging infectious diseases and related concerns, such as influenza, Ebola, Zika, and antimicrobial resistance. NIH-supported research on infectious diseases and biodefense covers a wide array of areas, from those that are disease-focused (the understanding, detecting, preventing, and treating of disease) to those areas that are people-focused (community engagement to address vaccine hesitancy and coordination centers to synergize researchers' efforts)

Research on infectious diseases and biodefense is primarily conducted and supported by NIAID. However, other NIH ICOs (including CC, FIC, NCATS, NCCIH, NCI, NEI, NHLBI, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA,

[1248] https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021
[1249] Mortality in the United States, 2020. https://www.cdc.gov/nchs/products/databriefs/db427.htm

NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NIMHD, NINDS, NINR, and NLM) also support research in this area, as do the *All of Us* Research Program, OAR, OBSSR, ODSS, OPA, OSC (NIH Common Fund), and ECHO within the NIH OD. NIH funding for Infectious Diseases was $6,313 million in FY 2019, $8,301 million in FY 2020, and $8,212 million in FY 2021. NIH funding for Biodefense was $2,353 million in FY 2019, $2,561 million in FY 2020, and $2,688 million in FY 2021.[1250] NIH funding for Coronaviruses was $2,355 million in FY 2020, and $1,922 million in FY 2021.

Vector-Borne Disease Research

The 21st Century Cures Act (P.L. 114-255, Sec. 2062 (a) and (b)) mandates that NIH conduct or support epidemiological, basic, translational, and clinical research related to vector-borne diseases, including tickborne diseases, and that it provide information on NIH actions with respect to tickborne diseases. In response to this mandate, Appendix C includes the following information on NIH actions in FY 2019, 2020, and 2021, regarding tickborne diseases and other vector-borne diseases:

- Epidemiological, basic, translational, and clinical research updates
- Committees convened
- Programs active
- Workshops held

Major Infectious Diseases

Infectious diseases can be caused by many different microorganisms, and NIH supports research to control and prevent diseases caused by virtually all human-infectious agents. Major infectious diseases, such as HIV/AIDS, malaria, tuberculosis, and viral hepatitis, significantly impact the health and well-being of millions of people around the world. NIH provides funding opportunities and a comprehensive set of resources for researchers that support basic research, preclinical development, and clinical evaluation, to better understand, prevent, treat, and improve the quality of life of patients with these diseases.

HIV/AIDS

The human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS). It can be transmitted during sexual intercourse, by sharing needles or syringes, or perinatally during pregnancy, childbirth, or breastfeeding. HIV infects a specific type of immune cell and is able to hide in cells, in the bloodstream, and in tissues, making it very difficult to cure. Recently, scientists have found that copies of the virus made by these cells could be neutralized by anti-HIV drugs, marking progress towards a widely accessible cure for HIV.[12511252]

[1250] https://report.nih.gov/funding/categorical-spending#/. Reporting for this category does not follow the standard RCDC process. The total amount reported is consistent with reporting requirements for this category to the U.S. Office of Management & Budget (OMB). The project listing includes non-project or other support costs associated with the annual total for this category. Additional information on this category is available at https://www.niaid.nih.gov/research/biodefense

[1251] Nixon CC, et al. *Nature* 2020 Feb;578(7793):160-165. PMID: 31969707.

[1252] McBrien JB, et al. *Nature* 2020 Feb;578(7793):154-159. Erratum in: *Nature* 2020 Feb 4. PMID: 31969705.

In FY 2021, NIH released the *NIH Strategic Plan for HIV and HIV-Related Research for FY 2021–2025.*[1253] This plan, developed by the Office of AIDS Research (OAR), provides a roadmap for the NIH HIV/AIDS research program to guide NIH's investment, building on scientific progress and opportunities for advancing HIV/AIDS research toward an end to the pandemic. As authorized in the *NIH Revitalization Act of 1993*, OAR allocates funds to nearly every NIH IC to support HIV/AIDS research that is aligned with the priorities outlined in the Plan. NIH funding for HIV/ AIDS was $3,037 million in FY 2019, $3,076 million in FY 2020 and $3,082 million in FY 2021.[1254]

Preventing HIV Transmission and Infection

Preventing new HIV transmissions is a key step toward ending the HIV/AIDS pandemic. While currently available HIV treatment and prevention tools have greatly reduced transmission of the virus, there remains a need for long-acting HIV prevention strategies that are acceptable and desirable to people from diverse communities worldwide.

Today, safe and effective anti-HIV treatment regimens, such as ART, allow people with HIV to suppress the amount of virus in the blood to a level so low that it is undetectable by standard tests. People with HIV who maintain an undetectable viral load by taking daily ART cannot sexually transmit the virus, a concept known as undetectable=untransmittable, or U=U.[1255] For those who are HIV-uninfected, numerous methods of preventing HIV acquisition are available, including pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), which are also daily regimens of ART.

Currently licensed PrEP medications (daily oral pills containing the HIV drugs tenofovir and emtricitabine) are highly effective at preventing HIV when taken as prescribed. However, maintaining a daily regime can be challenging. A long-acting form of PrEP could offer a less frequent and more discreet option that may be more desirable for some people. Findings from two NIAID-funded clinical studies showed that a PrEP regimen containing an investigational long-acting form of the HIV drug cabotegravir injected once every eight weeks was safe and more effective than a daily oral PrEP regimen at preventing HIV transmission among cisgender men who have sex with men and transgender women who have sex with men,[1256] and among a group of cisgender women in southern and east Africa.[1257] This finding in cisgender women marks the first time a large-scale clinical trial has shown a long-acting injectable form of HIV prevention to be highly effective for this population group. These studies supported FDA approval of Apretude

---

[1253] *NIH Strategic Plan for HIV and HIV-Related Research FY 2021-2025.* https://www.oar.nih.gov/sites/default/files/NIH_StrategicPlan_FY2021-2025.pdf

[1254] https://report.nih.gov/funding/categorical-spending#/. The total for AIDS research includes both extramural and intramural research (including Research Management and Support, Management Fund, Program Evaluation, and Service & Supply Fund), research training, contracts, and buildings and facilities. Unlike other RCDC categories, the total for AIDS research is coded to match the specified allocated budget for HIV/AIDS activities. As a result, the reported total for AIDS-related research is not comparable to spending reported for other RCDC categories. More information on AIDS and AIDS-related research is available at https://www.oar.nih.gov/hiv-policy-and-research.

[1255] https://www.niaid.nih.gov/diseases-conditions/hivaids

[1256] https://www.niaid.nih.gov/news-events/long-acting-injectable-form-hiv-prevention-outperforms-daily-pill-nih-study

[1257] https://www.niaid.nih.gov/news-events/statement-nih-study-finds-long-acting-injectable-drug-prevents-hiv-acquisition

(cabotegravir extended-release injectable suspension) in December 2021 for use of PrEP in adults and adolescents (weighing at least 35 kilograms or 77 pounds).[1258]

NIMH supports research aimed at reducing HIV/AIDS incidence through the development, testing, and implementation of new and improved prevention strategies, as well as improving health outcomes of individuals with HIV through improved linkage to care and adherence to effective treatments. In 2019, NIMH-funded researchers demonstrated the effectiveness of using algorithms that analyze electronic health records to help physicians identify patients at risk for HIV who may benefit from PrEP, which significantly reduces the risk of HIV acquisition.[1259] Other NIMH-funded researchers analyzed data from postpartum women in South Africa and found an association between intimate partner violence and elevated viral loads.[1260] In 2020, NIMH-funded studies pointed to the need for further development of tools to eradicate HIV from biological reservoirs in the central nervous system, where the virus may evade detection and treatment.[1261]

Broadly neutralizing antibodies, which arise naturally in some people with HIV and can stop a wide range of HIV strains from infecting human cells in the laboratory, are considered promising candidates for long-acting HIV prevention. These antibodies could be given directly by either infusion or injection or could be elicited by an HIV vaccine candidate. The Antibody-Mediated Prevention Studies aimed to establish whether infusions of a broadly neutralizing antibody called VRC01 are safe, tolerable, and effective at preventing HIV transmission. Two NIAID-funded multinational trials included more than 4,600 participants and found that VRC01 delivered intravenously once every eight weeks, safely and effectively prevented transmission of HIV strains known to be sensitive to the antibody.[1262] However, VRC01 did not significantly reduce overall HIV transmission after 80 weeks among participants, due to the prevalence of resistant HIV strains that could escape neutralization by the antibody and cause infection.[1263] However, these study findings did provide proof-of-concept that broadly neutralizing antibodies can be effective, and they suggest that while VRC01 alone does not offer sufficient protection against a broad range of HIV strains, combinations of antibodies may provide broader, more potent protection and have a longer half-life.

Improving HIV/AIDS Treatment

With research advances in ART, HIV/AIDS is no longer a uniformly fatal disease, but rather a manageable, chronic condition for many HIV-infected individuals. NIH continues to conduct and support biomedical and behavioral research to develop new and more effective therapeutic products, drug classes, and drug combinations that are safe, effective, and acceptable to the patient populations who need them.

[1258] https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention

[1259] Marcus JL, et al. *The Lancet HIV*. 2019;6(10):e688-e695. PMID: 31285183.

[1260] Hatcher AM, et al. *AIDS*. 2020;35(5):791-799. PMID: 33587440.

[1261] https://www.nimh.nih.gov/news/science-news/2020/brain-cells-can-harbor-and-spread-hiv-virus-to-the-body.

[1262] Corey L, et al. *N Engl J Med* 2021 Mar 18;384(11):1003-1014. PMID: 33730454

[1263] https://www.nih.gov/news-events/news-releases/antibody-infusions-prevent-acquisition-some-hiv-strains-nih-studies-find

Individuals with perinatally-acquired HIV (HIV transmitted from mother to child in utero or during birth or breastfeeding) now survive to adulthood with appropriate treatment, but they may still face developmental consequences of prolonged HIV infection and associated comorbidities, co-infections, and other complications (CCCs). In FY 2020, study results showed that children with perinatally-acquired HIV did not perform as well as their peers without HIV on tests measuring cognitive ability, motor function, and attention.[1264] All children with HIV were on ART during the study and about three-quarters achieved viral suppression. Researchers found that participants with HIV had poorer performance on neuropsychological evaluations compared to participants without HIV.[1265] Notably, participants with HIV had significantly less improvement over time in planning and reasoning abilities than their HIV-uninfected peers. These findings suggest that some children may experience neuropsychological difficulties over time, even when HIV infection is well controlled. Together, these data highlight the need to investigate the underlying mechanisms of these neuropsychological challenges, and to develop additional interventions to support children who acquire HIV early in life. This is the goal of the Pediatric HIV/AIDS Cohort Study,[1266] which addresses the long-term safety of fetal and infant exposure to ART and the effects on adolescents of perinatally-acquired HIV infection. Support for this important study was continued in FY 2020.[1267]

Many factors can influence adherence to ART, including characteristics of the prescribed daily regimen. Simple, once-daily regimens with few side effects or toxicities are associated with higher levels of adherence. During FY 2019–2021, NIH continued to work to improve anti-HIV treatment and to develop long-acting therapies that may serve as alternatives to a daily ART regimen.

Regular infusions of an antibody that blocks the HIV binding site on human immune cells may have suppressed levels of HIV for up to four months in people undergoing a short-term pause in their ART regimens.[1268] Results of this Phase2 clinical trial, open-label study indicate the antibody, known as UB-421, was safe and did not induce the production of antibody-resistant HIV.[1269] Volunteers with well-controlled HIV infection discontinued their normal regimens of daily oral ART at the time of their first infusion or one week later, depending on their ART regimen. Another group of study participants received regular weekly infusions of UB-421, and a third group received higher-dose infusions every other week. At the end of the 8- or 16-week treatment period, all volunteers restarted their previous ART regimen and were evaluated in follow-up visits up to eight weeks later.

In a range of experiments, scientists reactivated resting immune cells that were latently infected with HIV or its monkey relative, simian immunodeficiency virus, in cells in the bloodstream and a variety of tissues in animals. As a result, the cells started making copies of the viruses, which could potentially be neutralized

[1264] https://www.niaid.nih.gov/news-events/children-hiv-score-below-hiv-negative-peers-cognitive-motor-function-tests
[1265] Boivin MJ, et al. *Clin Infect Dis* 2020 Oct 23;71(7):e105-e114. PMID: 31848582.
[1266] RFA-HD-20-002. https://grants.nih.gov/grants/guide/rfa-files/rfa-hd-20-002.html
[1267] https://www.nichd.nih.gov/research/supported/phacs
[1268] https://www.nih.gov/news-events/news-releases/novel-antibody-may-suppress-hiv-four-months
[1269] Wang CY, et al. *N Engl J Med* 2019 Apr 18;380(16):1535-1545. PMID: 30995373.

by anti-HIV drugs and the immune system.[1270] This advance marks progress toward a widely accessible cure for HIV.

In addition to ART regimens that directly target the virus, people with HIV may also receive therapy for those CCCs that are associated with well-controlled HIV infection. These include medications to treat and prevent infections commonly seen among people with HIV, such as viral hepatitis and tuberculosis, as well as noninfectious conditions, such as cardiovascular disease, certain cancers, and neurological disorders.

A clinical trial funded by the NIH has found that for women with HIV, treatment with the antibiotic isoniazid to prevent TB was similarly safe if begun during pregnancy or 12 weeks after delivery. However, there was significantly greater risk of poor health outcomes and death for the fetuses and newborns of these women if isoniazid preventive therapy began during pregnancy, than if it began 12 weeks after delivery.[1271] This finding is concerning and merits research into alternative approaches to TB preventive therapy in pregnant women, according to the study investigators.

Many people with HIV on ART have viral genetic material in the cells of their cerebrospinal fluid (CSF), and these individuals are more likely to experience memory and concentration problems.[1272] A study of 69 individuals on long-term ART found that nearly half of the participants had persistent HIV in cells in their CSF, and 30 percent of this subset experienced neurocognitive difficulties.[1273] These findings suggest that HIV can persist in the nervous system even when the virus is suppressed in a patient's blood with medication.

Non-alcoholic fatty liver disease, or NAFLD, frequently occurs along with HIV infection, affecting as many as 25 percent of people with HIV in the developed world.[1274] However, no effective treatments currently exist to treat the condition, which is a risk factor for progressive liver disease and liver cancer. In a clinical study, NIAID researchers and collaborators found that the injectable hormone tesamorelin reduces liver fat and prevents liver fibrosis (scarring) in people with HIV.[1275] Given these positive results, investigators suggest expanding the indication for tesamorelin to include people with HIV who have been diagnosed with NAFLD. They also recommend additional research to determine if tesamorelin could contribute to long-term protection against serious liver disease in people without HIV.

An increasing number of people with HIV have a need for kidney transplants, which are often in short supply. Starting with data from transplants beginning in 2008, researchers followed 51 study participants with HIV who received kidney transplants from deceased donors with HIV in South Africa.[1276] The observational study showed that people with HIV who received kidney transplants from deceased donors

---

[1270] https://www.niaid.nih.gov/news-events/nih-supported-scientists-reverse-hiv-and-siv-latency-two-animal-models

[1271] https://www.niaid.nih.gov/news-events/women-hiv-tb-preventive-therapy-poses-greater-risk-pregnancy-postpartum

[1272] https://www.niaid.nih.gov/news-events/persistent-hiv-central-nervous-system-linked-cognitive-impairment

[1273] Spudich S, et al. *J Clin Invest* 2019 Jul 15;129(8):3339-3346. PMID: 31305262.

[1274] https://www.niaid.nih.gov/news-events/drug-reverses-signs-liver-disease-people-living-hiv

[1275] Stanley TL, et al. *Lancet HIV* 2019 Dec;6(12):e821-e830. PMID: 31611038.

[1276] https://www.niaid.nih.gov/news-events/most-kidney-transplants-between-people-hiv-have-long-term-success

with HIV had high rates of overall survival and kidney graft survival after five years.[1277] These results provide additional evidence that organs from donors with HIV could be a new donation source for people with both HIV and end-stage kidney disease.

Currently, the southern U.S. has the highest rates of new HIV diagnoses, the largest percentage of people with HIV, and the most Americans dying from the disease. Given the increase of the HIV epidemic in the southern U.S. and the availability of evidence-based self-management tools (e.g., smartphone applications), NIH researchers conducted a survey in Birmingham, Alabama, to better understand the symptom profile and use of technology by people with HIV who sought services from a community-based organization.[1278] The survey identified frequently reported symptoms, including muscle aches or joint pain, fatigue, sleep difficulties, neuropathy, and depressive symptoms. The researchers found that the majority of survey participants had access to smartphones, providing a strong scientific premise to support the feasibility of a mobile-delivered symptom self-management tool in various geographic regions with large numbers of people with HIV.

Clinical practice guidelines are evidence-based recommendations on how to diagnose and treat a medical condition. Five federally approved clinical practice guidelines for HIV/AIDS are updated frequently by five panels of clinical experts in HIV treatment and care under the auspices of the OAR Advisory Council (OARAC).[1279] The panels and the corresponding guidelines that they develop include: Adult and Adolescent Antiretroviral, Adult and Adolescent Opportunistic Infections, Pediatric Antiretroviral, Pediatric Opportunistic Infections, and Perinatal. In FY 2020, in response to the COVID-19 pandemic, the OARAC expert panel developed the first version of the *Interim Guidance for COVID-19 and Persons with HIV*. In FY 2021, the Pediatric Opportunistic Infections panel underwent a rescoping effort to evaluate content and alignment with the contemporary needs of clinical providers treating and caring for children with HIV.

Community Engagement

During FY 2019–2021, NIH regularly obtained input from multiple communities to ensure that the overall NIH HIV research program and priorities are responsive to emerging scientific advances, changing dynamics of the pandemic, and the diverse needs of communities.

In FY 2020, OAR published the *HIV Stakeholder Outreach and Engagement Report (June 2018-February 2020)*.[1280] To develop the report, OAR sought and received input from the NIH AIDS Executive Committee, OARAC, individuals from academia, community-based organizations, clinical care settings, public health agencies, and advocacy and outreach organizations who responded to two Requests for Information (RFIs), and/or who participated in listening sessions, site visits, and community conversations. These sessions occurred mainly in the U.S., with a few meetings and site visits in Mexico and South Africa, which allowed input from key international stakeholders. In FY 2021, OAR conducted additional listening sessions throughout the U.S. to provide an open and transparent forum for stakeholders to communicate

[1277] Selhorst P, et al. *N Engl J Med* 2019 Oct 3;381(14):1387-1389. PMID: 31577883.
[1278] Schnall R,et al. *J Assoc Nurses AIDS Care* 2020 Jan-Feb;31(1):42-50. PMID: 30908348.
[1279] https://clinicalinfo.hiv.gov/en
[1280] HIV Stakeholder Outreach and Engagement Report (June 2018-February 2020). https://www.oar.nih.gov/sites/default/files/2020_OAR_Stakeholder_Outreach_Report_12-18-21_508.pdf

their needs from a local and regional point of view. Findings were published in the *Second HIV Stakeholder Outreach and Engagement Report (September 2020-July 2021)*.[1281]

Malaria

Malaria is caused by *Plasmodium* parasites, which are transmitted to people through the bite of an infected mosquito. Malaria can cause infected people to become sick with high fever, chills, and flu-like illness. It can also cause death. According to the WHO, an estimated 229 million cases of malaria occurred worldwide in 2019, resulting in an estimated 409,000 deaths, mostly in children in sub-Saharan Africa.[1282] Although substantial progress has been made in the fight to control and eliminate malaria, the mosquito-borne disease remains a significant public health problem.

So far, no licensed or experimental malaria vaccine that has completed phase 3 testing provides more than 50 percent protection from the disease over the course of a year or longer. Two U.S. phase 1 clinical trials of a novel candidate malaria vaccine have found that the regimen conferred unprecedentedly high levels of durable protection when volunteers were later exposed to disease-causing malaria parasites.[1283] The vaccine combines live parasites with either of two widely used antimalarial drugs, an approach termed chemoprophylaxis vaccination.[1284] A phase 2 clinical trial of the vaccine is now underway in Mali, a malaria-endemic country. If the approach proves successful there, chemoprophylaxis vaccination may prove to be a strong strategy for control of global malaria.

Prior laboratory and animal studies have demonstrated that antibodies can prevent malaria by neutralizing the parasites in the skin and blood before they can infect liver cells. NIH scientists discovered and developed a new monoclonal antibody that safely prevented malaria for up to nine months in people who were exposed to the parasite.[1285] The small, carefully monitored clinical trial conducted by the NIAID Vaccine Research Center's Clinical Trials Program is the first to demonstrate that a monoclonal antibody can prevent malaria in people.[1286] Additional research is needed to confirm and extend this finding before it can be applied globally.

Please see Appendix C for more information on malaria research.

Tuberculosis

Tuberculosis (TB) is a contagious disease caused by infection with *Mycobacterium tuberculosis* (Mtb) bacteria. TB is the second leading infectious cause of death worldwide, after COVID-19. Over the past 200 years, TB has claimed the lives of more than one billion people—more deaths than from malaria,

[1281] HIV Stakeholder Outreach and Engagement Report (September 2020-July 2021). https://www.oar.nih.gov/sites/default/files/OAR-Phase2-Stakeholders-Report-2021-508.pdf
[1282] https://www.who.int/news-room/fact-sheets/detail/malaria
[1283] https://www.niaid.nih.gov/news-events/investigational-malaria-vaccine-gives-strong-lasting-protection
[1284] Mwakingwe-Omari A, et al. *Nature*. 2021 Jul;595(7866):289-294. PMID: 34194041.
[1285] https://www.nih.gov/news-events/news-releases/monoclonal-antibody-prevents-malaria-small-nih-trial
[1286] Gaudinski MR, et al. *N Engl J Med.* 2021 Aug 26;385(9):803-814. PMID: 34379916

influenza, smallpox, HIV/AIDS, cholera, and plague combined.[1287] Although TB treatment exists, drug resistance is a continued threat.

To provide patients with TB with the treatment that they need, healthcare providers must have accurate diagnostic tests. However, the standard sample collection methods used to diagnose TB in children are invasive, uncomfortable, and often not practical in limited-resource settings. Previous research has found that collecting samples using less invasive methods can lead to inaccurate results in children. Researchers tested whether combining test results from multiple collection methods could be as accurate as the existing methods for diagnosis.[1288] These NICHD-supported researchers tested several samples from 294 children in Kenya who were under five years old, then compared the results of tests from invasive and less invasive sample collection methods. The researchers found that combining results from tests using stool or urine samples and tests using samples from the back of the nose and throat, which they collected using less invasive methods, provided an accurate diagnosis of TB. They found that combining the results of tests that used two samples from the nose and throat was also effective and adding these less invasive testing methods to standard testing methods was even more effective in diagnosing TB in children. The results of this study may lead to easier TB diagnosis and could increase the number of children who receive timely treatment for TB in limited-resource settings.

Increasingly, Mtb is resistant to conventional antibiotic treatments. While the Bacille Calmette-Guerin (BCG) vaccine—the world's only licensed TB vaccine developed over a century ago—can prevent TB in infants and young children, no vaccine is approved to prevent TB in older children and adults. Therefore, more effective tools to prevent and treat TB are needed.

The BCG vaccine protects babies from a form of the disease called disseminated TB, but it is far less effective at preventing pulmonary TB, the major cause of illness and deaths, in teens or adults. Researchers have shown that simply changing the dose and route of administration from intradermal (skin) to intravenous greatly increases the vaccine's ability to protect rhesus macaques from infection following exposure to Mtb.[1289,1290] The findings provide a new understanding of the mechanisms of BCG vaccine-elicited protection against TB infection and disease.

Results from an international, randomized, controlled clinical trial indicate that a four-month daily treatment regimen containing high-dose rifapentine with moxifloxacin is as safe and effective as the existing standard six-month daily regimen at curing drug-susceptible TB.[1291] This regimen is the first successful short-course treatment regimen for drug-susceptible TB in almost 40 years. Shortening treatment for TB can benefit patients, families, healthcare providers, and health systems. The availability

[1287] https://www.niaid.nih.gov/diseases-conditions/tuberculosis
[1288] Song R, et al. *JAMA Pediatr.* 2021 May 1;175(5):e206069. PMID: 33616611.
[1289] https://www.niaid.nih.gov/news-events/changed-route-immunization-dramatically-improves-efficacy-tb-vaccine
[1290] Darrah PA, et al. *Nature.* 2020 Jan;577(7788):95-102. PMID: 31894150.
[1291] https://www.niaid.nih.gov/news-events/landmark-tb-trial-identifies-shorter-course-treatment-regimen

of shorter regimens enables patients to be cured faster, and has the potential to reduce treatment costs, improve patient quality of life, increase completion of therapy, and reduce drug resistance.

In FY 2019, researchers discovered that a class of immune cells called innate lymphoid cells (ILCs) mediate the body's initial defense against TB.[1292] Identified only in the past decade, ILCs can initiate quick, nonspecific responses against pathogens and also mount protective immune responses directed against specific pathogens. In this study, researchers observed that among people who were infected with Mtb, a subset of ILCs moved from the blood to the lungs, where TB infections frequently take hold.[1293] Because ILCs seem to protect early in TB, investigators suggest that probing the newly described pathway may yield novel approaches to TB treatment and prevention.

For people with weakened immune systems, such as those with HIV infection, the risk of developing TB disease after Mtb infection is much higher than for those with normal immune systems. In FY 2019, NIH scientists published clinical trial results to help clarify how to safely prevent TB in women with HIV who are pregnant or have recently given birth, are taking ART, and live where TB is highly prevalent.[1294,1295] The trial results showed that antibiotic treatment to prevent TB was similarly safe for the women if begun during pregnancy or 12 weeks after delivery. However, there was significantly greater risk of poor health outcomes and death for the fetuses and newborns of these women if antibiotic preventive therapy began during pregnancy than if it began 12 weeks after delivery. This finding is concerning and merits research into alternative approaches to TB preventive therapy in pregnant women, according to the study investigators.

Viral Hepatitis

Viral hepatitis is an infection that causes liver inflammation and damage. Several different viruses cause hepatitis, including hepatitis A, B, C, D, and E. The hepatitis A and E viruses typically cause acute infections. The hepatitis B, C, and D viruses can cause acute and chronic infections.

Hepatitis B Virus

Acute hepatitis B is a short-term infection. Some people have symptoms, which may last several weeks. In some cases, symptoms last up to six months. If the body is not able to fight off the virus, chronic or long-lasting hepatitis B infection occurs. It is estimated that 820,000 people worldwide die from complications from hepatitis B infection each year.[1296] An individual's chances of developing chronic hepatitis B are greater if they are infected with the virus as a young child. The hepatitis B vaccine has been available since the 1980s, and, in 1991, doctors began recommending that children in the U.S. receive the hepatitis B vaccine. This highly effective vaccine has been available for nearly 40 years, yet millions of people worldwide continue to become infected with the virus.[1297] In FY 2019, NIH released the *Strategic*

[1292] https://www.niaid.nih.gov/news-events/immune-cells-play-unexpected-role-early-tuberculosis-infection
[1293] Ardain A, et al. *Nature.* 2019 Jun;570(7762):528-532. Erratum in: *Nature*. 2019 Jul 24: PMID: 31168092.
[1294] https://www.niaid.nih.gov/news-events/women-hiv-tb-preventive-therapy-poses-greater-risk-pregnancy-postpartum
[1295] Gupta A, et al. *N Engl J Med*. 2019 Oct 3;381(14):1333-1346. PMID: 31577875.
[1296] https://www.cdc.gov/globalhealth/immunization/diseases/hepatitis-b/data/fast-facts.html
[1297] https://www.cdc.gov/hepatitis/hbv/pdfs/hepbatrisk.pdf

Plan for Trans-NIH Research to Cure Hepatitis B,[1298] which outlines NIH's efforts to intensify ongoing hepatitis B virus research with the goals of developing a cure and improving scientific understanding of the virus while creating improved strategies for screening and treating patients.[1299]

In FY 2019–2021, the Hepatitis B Research Network[1300] completed multicenter studies of the natural history, pathogenesis, diagnosis, and treatment of chronic hepatitis B in adults and children living in North America. Additionally, the network implemented a longitudinal observational database of children 2-17 years of age and a longitudinal observational database of adults at least 18 years of age. In FY 2019, the network published results from two clinical trials of a combination drug therapy, one in adults[1301] and another in children,[1302] which showed that this particular treatment approach to chronic hepatitis B was well-tolerated but of limited benefit, suggesting that a combination of three or more agents directed at different viral targets may be required. In FY 2020, network investigators reported results from studies defining different chronic hepatitis B presentations in children[1303] and assessing maternal knowledge of hepatitis B virus transmission to infant during delivery.[1304] In FY 2021, a network-supported study was published that followed children with chronic hepatitis B over time, showing that many were at risk for progressive liver disease and did not receive treatment.[1305]

NIH scientists and their collaborators found that hepatitis B virus-associated acute liver failure (HBV-ALF), a rare condition that can turn fatal within days without liver transplantation, results from a highly mutated HBV variant and an unusual immune response in the patient's liver.[1306] The scientists identified processes that are distinctive to HBV-ALF cases compared with cases of classic acute HBV infection. The HBV-ALF findings were consistent among samples taken from all patients studied, an important validation because virtually no studies have been done on the molecular pathogenesis of HBV-ALF in the liver.[1307] This study provides a model of how the disease develops and will lead to new diagnostic, treatment, and prevention strategies.

Hepatitis C Virus

Hepatitis C is one of the most common bloodborne infections in the U.S. Although it may not cause any symptoms in its early stages, untreated chronic infections can lead to severe liver damage, cancer, and death. About 75 to 85 percent of people with acute hepatitis C will develop chronic hepatitis C.[1308]

[1298] *Strategic Plan for Trans-NIH Research to Cure Hepatitis B*. https://www.niaid.nih.gov/sites/default/files/Trans-NIH-Hep-B-Strategic-Plan-2019.pdf

[1299] https://www.nih.gov/news-events/news-releases/nih-strategic-plan-details-pathway-achieving-hepatitis-b-cure

[1300] https://www.hepbnet.org/

[1301] Feld JJ, et al. *Hepatology* 2019 Jun;69(6):2338-2348. PMID: 30549279.

[1302] Rosenthal P, et al. *Hepatology* 2019 Jun;69(6):2326-2337. PMID: 30318613.

[1303] Schwarz KB, et al. *J Pediatr Gastroenterol Nutr.* 2019 Nov;69(5):588-594. PMID: 31436702.

[1304] Lisker-Melman M, et al. *Ann Hepatol.* 2020 Jul-Aug;19(4):388-395. PMID: 32507734.

[1305] Ling SC, et al. *J Pediatr*. 2021 Oct;237:24-33.e12. PMID: 34022250.

[1306] https://www.nih.gov/news-events/news-releases/nih-scientists-illuminate-causes-hepatitis-b-virus-associated-acute-liver-failure

[1307] Chen Z, et al. *Proc Natl Acad Sci U S A.* 2018 Nov 27;115(48):E11369-E11378. PMID: 30420516.

[1308] https://www.niddk.nih.gov/health-information/liver-disease/viral-hepatitis/hepatitis-c

Concerningly, infections are on the rise among young adults, largely due to exposure resulting from shared drug-injectables. No vaccine is currently available to prevent hepatitis C infection, so early diagnosis and treatment is essential to prevent liver damage.

It has been difficult to develop a vaccine for hepatitis C because the virus has many different strains and subtypes, and a safe and effective vaccine would need to protect against all or most of these strains and subtypes. Scientists from NIAID recently published the structure of a key protein on the surface of the hepatitis C virus and described how it interacts with its receptor found on some human cells.[1309] The findings provide new leads for developing a vaccine for hepatitis C.

Scientists in the NIDDK's Intramural Research Program published a study in FY 2020 concluding that animal models infected with different hepatitis C viral subtypes, including a drug-resistant one, responded well to a new combination treatment.[1310] This could represent the next generation of hepatitis C treatments, with benefits such as shorter treatment length, improved response across viral subtypes, and lower chance of developing viral drug resistance.

Other Major Infectious Diseases

In addition to HIV/AIDS, malaria, TB, and viral hepatitis, NIH supports research on many other major infectious diseases, several of which are outlined here.

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a herpesvirus that causes infectious mononucleosis and is associated with certain cancers of epithelial cells, which form the lining of the body's surfaces, as well as Burkitt and Hodgkin lymphomas, which are cancers of the immune system's B cells. Worldwide, about 200,000 cases of EBV-associated cancers occur annually, resulting in 140,000 deaths.[1311] Currently, there is no licensed vaccine for EBV.

A research team led by NIAID scientists has determined how several antibodies induced by EBV block infection of cells grown in the laboratory.[1312] The scientists used this information to develop novel vaccine candidates that, in animals, elicited potent anti-EBV antibody responses that blocked infection of cell types involved in EBV-associated cancers.[1313] The team is planning to further develop one of the vaccine constructs to eventually test in clinical trials.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) infects the lungs and breathing passages, and, in the U.S., nearly all children have been infected with RSV by the age of two. In healthy people, symptoms of RSV infection are usually mild and resolve within a week. However, RSV can cause serious illness or death in vulnerable individuals, including premature and very young infants, children with chronic lung disease or congenital

[1309] Kumar A, et al. *Nature.* 2021 Oct;598(7881):521-525. PMID: 34526719.
[1310] Ma CD, et al. *Nat Microbiol*. 2020 Dec;5(12):1532-1541. PMID: 32868923.
[1311] Shannon-Lowe C and Rickinson A. *Front Oncol.* 2019; 9: 713. PMID: 31448229.
[1312] https://www.niaid.nih.gov/news-events/nih-researchers-make-progress-toward-epstein-barr-virus-vaccine
[1313] Bu W, et al. *Immunity.* 2019 May 21;50(5):1305-1316.e6. PMID: 30979688.

heart disease, and people who are over age 65. In the U.S., RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lungs) in children younger than one year old, and it causes approximately 58,000 hospitalizations annually among children under the age of five. RSV infection is estimated to also cause about 14,000 annual deaths of adults over the age of 65 in the U.S.[1314] The health burden of RSV has long been underappreciated and a vaccine to prevent RSV is a long-sought goal that has eluded scientists for decades.

A novel experimental vaccine against RSV has shown early promise in a phase 1 clinical trial.[1315] The candidate, DS-Cav1, was engineered and developed by researchers at NIAID, who were guided by their atomic-level studies on the shape of an RSV protein. An interim analysis of study data showed that one dose of the investigational vaccine prompted large increases in RSV-neutralizing antibodies that were sustained for several months.[1316] Scientists hope that the results of this trial using a structure-based strategy for vaccine design will bring this long-sought goal into reach.

Sepsis

Sepsis is a person's overwhelming or impaired whole-body immune response to an infection or an injury to the body, or some other factor that provokes such a response. It is a serious condition and a leading cause of readmittance to the hospital and death in hospitals. Sepsis occurs unpredictably and can progress rapidly. In severe cases, one or more organ systems fail. In the worst cases, blood pressure drops, the heart weakens, and the patient spirals toward septic shock. Once this happens, multiple organs (lungs, kidneys, liver) may quickly fail, and the patient can die.

NIGMS supports a major portfolio of sepsis research that includes both fundamental and clinical studies and those that emphasizes the person's response to sepsis rather than its initial triggers (e.g., infection or injury). In an effort to optimize NIGMS' sepsis research portfolio, the IC has sought input from key community members on novel ideas and strategies by which to address the challenges and opportunities inherent in this evolving field. In addition, it has convened a working group of its Advisory Council to help guide the IC on how to accelerate advances in both the rapid detection and treatment of this condition. In FY 2019, NIGMS released a notice outlining the IC's priorities for sepsis research.[1317] In FY 2021, NIGMS released a funding announcement exploring the scientific value of existing or new sepsis human biospecimen collections.[1318]

In FY 2021, NICHD released a funding announcement to support interdisciplinary community-engaged research designed to reduce or eliminate infections and sepsis as causes of pregnancy-related (or pregnancy-associated) morbidity and mortality in regions of the U.S. with high rates of maternal

[1314] https://www.cdc.gov/rsv/research/index.html
[1315] https://www.niaid.nih.gov/news-events/experimental-respiratory-syncytial-virus-vaccine-prompts-antibody-surge
[1316] Crank MC, et al. *Science.* 2019 Aug 2;365(6452):505-509. PMID: 31371616.
[1317] Notice of Information, NOT-GM-19-054. https://grants.nih.gov/grants/guide/notice-files/NOT-GM-19-054.html
[1318] Funding Opportunity Announcement, R21/R33 Phased Innovation Award, PAR-021-077. https://grants.nih.gov/grants/guide/pa-files/PAR-21-077.html

mortality.[1319] The initiative requires an emphasis on disparities research inclusive of age, geographic, socioeconomic, and racial or ethnic disparities, including people with disabilities.

Tickborne Diseases

Tickborne diseases can be caused by viruses, bacteria, or parasites. Most people become infected through tick bites during the spring and summer months. The incidence of tickborne infections in the U.S. has risen significantly within the past decade. Due to this increase, it is becoming more important for public health officials and scientists to improve their understanding of the pathogenesis of the infections, and to design improved diagnostics and develop preventive vaccines for tickborne illnesses. In 2019, NIH released the NIH Strategic Plan for Tickborne Disease Research, which proposes building on current NIH-wide efforts to better understand the complex interplay among the host, tick, and pathogen factors that contribute to tickborne diseases and the body's defenses against them.[1320]

The salivary glands of some tick species could become important research tools for studying how viruses are transmitted from ticks to mammals, and for developing preventive medical countermeasures. Tick salivary glands usually block transmission, but in FY 2019, a study conducted by scientists at NIAID focused on the role of salivary glands in spreading flaviviruses from black-legged ticks (also known as deer ticks, *Ixodes scapularis*) to mammals.[1321] Flaviviruses include dengue virus, Zika virus, West Nile virus, yellow fever virus, Powassan virus and several other viruses. In examining the molecular interactions between black-legged ticks and mammals, the NIAID scientists learned that flaviviruses reproduce in specific locations in tick salivary gland cultures.[1322] This could explain why virus transmission occurs so quickly. They also noted that only certain types of salivary gland cells are infected, and they identified a specific tick gene that is involved in infection. These findings help identify transmission pathways that potentially could be blocked with a countermeasure.

Also spread by black-legged ticks, Lyme disease is caused by *Borrelia burgdorferi*, a spiral-shaped bacterium. Current Lyme disease diagnostic tests can miss an infection if performed too early. Currently, CDC recommends a two-step blood test for diagnosing Lyme disease based on antibodies against the bacteria. These tests require specialized laboratory equipment and can require days or weeks to return results. Researchers are developing a simpler, faster, more sensitive test that could be used at the point-of-care during a single visit to a healthcare provider.[1323] Researchers developed an assay, which uses several biomarkers to detect Lyme disease infection, and it is more sensitive than current tests at diagnosing Lyme disease early after suspected infection.[1324] These results open the possibility of developing a point-of-care test for Lyme disease.

[1319] Funding Opportunity Announcement, RFA-HD-21-033. https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-21-033.html

[1320] https://www.niaid.nih.gov/sites/default/files/NIH-Strategic-Plan-Tickborne-Disease-Research-2019.pdf

[1321] https://www.nih.gov/news-events/news-releases/nih-scientists-explore-tick-salivary-glands-tool-study-virus-transmission-infection

[1322] Grabowski JM, et al. *mBio.* 2019 Jan 29;10(1):e02628-18. PMID: 30696737.

[1323] https://www.niaid.nih.gov/news-events/scientists-work-toward-rapid-point-care-diagnostic-test-lyme-disease

[1324] Arumugam S, et al. *J Clin Microbiol.* 2019 Nov 22;57(12):e01142-19. PMID: 31597750.

Please see Appendix C for more information on research on tickborne diseases.

Emerging Infectious Diseases and Biodefense (Including Seasonal and Pandemic Influenza)

It is not possible to predict when a new or re-emerging infectious disease will appear and how dangerous it may become. NIH must remain vigilant and prepared with prevention strategies, diagnostics, and medical countermeasures, such as the ability to launch rapid vaccine production and dissemination. Readiness for such occurrences also involves ongoing basic research on microorganisms and the human immune system.

Influenza

Seasonal influenza, or the flu, is a highly contagious respiratory disease caused by any of several human influenza viruses that circulate globally and cause annual outbreaks of varying severity. Influenza viruses infect the nose, throat, and lungs and produce symptoms that include sudden fever, extreme fatigue, coughing, chills, and muscle aches. Serious complications include pneumonia. Each year, the flu causes millions of illnesses worldwide and kills many thousands of people. It is especially dangerous for people who are very young or old or who have other conditions, such as heart disease or asthma.

Pandemic influenza occurs when a new, non-human flu virus emerges from an avian or other animal source with the capacity to spread readily from person to person. Because such viruses have not previously circulated in humans, there is no pre-existing human immunity to them, and virus spread can result in disease outbreaks. The most recent influenza pandemic occurred in 2009.

Influenza is challenging for scientists to study because there are hundreds of strains that are classified into four main categories: A through D, although D is not known to infect people. Influenza A virus is the group that most commonly causes illness in humans, and it has been the source of all major influenza pandemics in modern history. Influenza type A can drift and shift through birds and animals, in other words, it emerges from animal infection with rearranged surface proteins that create different strains of the virus. Those surface proteins, which can combine in different ways to create an assortment of influenza virus type A strains, are called hemagglutinin (HA) and neuraminidase (NA) glycoproteins. HA enables the flu virus to enter a human cell and initiate infection, while NA allows newly formed flu viruses to exit the host cell and multiply throughout the body.[1325]

NIAID scientists and colleagues designed an influenza vaccine, called FluMos-v1, using 20 HA antigen components displayed in a repeating pattern on scaffolds made of self-assembling particles.[1326] These repeated patterns send a strong "danger" signal to the immune system and prompt vigorous antibody responses. In animal studies, this flu vaccine far outperformed the standard flu vaccine in its ability to elicit protective antibodies to influenza types that were not included in the vaccine.[1327] FluMos-v1 is being tested in a phase 1 clinical trial.[1328]

[1325] https://www.cdc.gov/flu/about/viruses/change.htm
[1326] https://www.niaid.nih.gov/news-events/nanoparticle-flu-vaccine
[1327] Boyoglu-Barnum S, et al. *Nature*. 2021 Apr;592(7855):623-628. PMID: 33762730.
[1328] https://www.niaid.nih.gov/news-events/nih-launches-clinical-trial-universal-influenza-vaccine-candidate

Scientists have discovered and characterized the structure of a naturally occurring human antibody that recognizes and disrupts HA, thereby disrupting the influenza virus's ability to enter a cell.[1329] The investigators determined that the antibody, FluA-20, binds tightly to an area on the head of the HA protein that is only very briefly accessible to antibody attack. In a series of experiments, they showed that FluA-20 can "reach into" an otherwise inaccessible part of the HA molecule and cause it to disrupt, thus preventing the spread of virus from cell to cell.[1330] This stem-like region of HA is less variable than the head of the viral particle, which is the region targeted by current seasonal influenza vaccines and by standard laboratory tests used to gauge a person's immune response to a particular strain of influenza. Another study focused on the HA stem assessed influenza virus transmission in Nicaraguan households, revealing new insights into the type of immune responses that may be protective against influenza virus infection.[1331] The findings could help scientists design more-effective influenza vaccines and antibody-based therapeutics that would be effective against many strains of influenza A virus. Similarly, vaccines and treatments that have been developed that target the HA stem might provide long-lasting protection against any influenza strain, potentially eliminating the need for annual seasonal influenza vaccination.

Researchers also looked at ways to disrupt NA to develop better treatments and vaccines against influenza. They isolated the antibodies from a person with the flu at five days after the onset of symptoms.[1332] They found that the antibodies had bound to NA glycoprotein and thus provided broad protection against several different strains of influenza when tested both in vitro and in mice.[1333] Additional testing is needed to support these early results.

In FY 2019–2021, researchers explored how different routes of vaccination and bodily systems affect immune responses to influenza and could be applied to other infectious diseases. NIAID investigators demonstrated in a phase 1 study[1334] that an experimental single-dose influenza vaccine was safe and produced a durable immune response. The investigational vaccine, called Ad4-H5-VTN, is an adenovirus vaccine designed to spur antibodies to the HA glycoprotein. It was administered intranasally, as an oral capsule, or via a tonsillar swab to non-pregnant people ages 18 to 49 years.[1335] The participants who received the vaccine intranasally or via tonsillar swab showed significantly higher HA-specific neutralizing antibody levels compared with the group receiving the vaccine capsule orally. Scientists believe this vaccine platform could be highly adaptable for use against other viruses, including HIV and SARS-CoV-2.

The normal human gut microbiome is a flourishing community of microorganisms, some of which can affect the human immune system. Researchers found that oral antibiotics, which can kill gut

[1329] https://www.niaid.nih.gov/news-events/human-antibody-reveals-hidden-vulnerability-influenza-virus
[1330] Bangaru S, et al. *Cell.* 2019 May 16;177(5):1136-1152.e18. PMID: 31100268.
[1331] Ng S, et al. *Nat Med.* 2019 Jun;25(6):962-967. PMID: 31160818.
[1332] https://www.niaid.nih.gov/news-events/broadly-protective-antibodies-could-lead-better-flu-treatments-and-vaccines
[1333] Stadlbauer D, et al. *Science.* 2019 Oct 25;366(6464):499-504. PMID: 31649200.
[1334] https://www.niaid.nih.gov/news-events/intranasal-influenza-vaccine-spurs-strong-immune-response-phase-1-study
[1335] Matsuda K, et al. *J Clin Invest.* 2021 Mar 1;131(5):e140794. PMID: 33529172.

microorganisms, can also alter the human immune response to seasonal influenza vaccination.[1336,1337] All study participants received a seasonal influenza vaccine. Half the participants in each group also received a five-day course of a broad-spectrum antibiotic regimen (consisting of neomycin, vancomycin, and metronidazole) by mouth before receiving the vaccine. By analyzing stool and blood serum samples taken at various times up to one year after vaccination, the researchers tracked the participants' immune response to the influenza vaccines, as well as the diversity and abundance of the organisms in their gut microbiomes. As expected, most participants who received antibiotics experienced reduced levels of gut bacteria. In addition, among the 2015–2016 participants who had little prior immunity to the seasonal influenza virus vaccine strains, a course of antibiotics hindered their immune responses to one of the three influenza virus strains in the vaccine, an H1N1 A/California-specific virus. This likely indicates that should they be exposed to this H1N1 virus after vaccination, these participants would be less protected against infection with that strain than people who had not received antibiotics, according to the authors.

Ebola Virus Disease

Ebola virus disease (EVD), first recognized in 1976 in the Democratic Republic of the Congo (DRC), is a serious and often fatal illness in humans and nonhuman primates. EVD ravaged West Africa in 2013, killing more than 10,000 people and severely straining regional socioeconomic stability.[1338] The NIH Clinical Center was one of four designated U.S. research hospitals to care for infected health care workers. NIH scientists worked to rapidly test a promising preventive vaccine and experimental Ebola treatment.

Four of the six known virus species of the Ebolavirus genus are known to cause disease in humans. NIH researchers study and monitor these ebolaviruses. For example, Reston Ebolavirus (RESTV) is known to infect monkeys, pigs, and humans, and can transit from pig to human. It is not known to cause disease in humans. In FY 2021, NIAID scientists confirmed that pigs that were experimentally infected with RESTV developed severe pneumonia with virus shedding from the upper respiratory tract.[1339] Researchers also determined that the age of the piglets at the time of infection did not change the course of disease. Due to these findings, the researchers concluded that RESTV should be considered a livestock pathogen with potential to affect other mammals, and perhaps even humans.[1340] Continuing studies in this project will examine whether co-infection with other swine viruses affects the ability of RESTV to cause severe disease in pigs, and whether pigs have a broad role in hosting ebolaviruses.

Multiple investigational Ebola vaccines have been tested in numerous clinical trials around the world. NIAID supported the development of the VSV-EBOV vaccine developed by Merck, which uses a genetically engineered version of vesicular stomatitis virus (VSV) to carry an Ebola virus gene insert (EBOV).

[1336] https://www.niaid.nih.gov/news-events/disrupting-gut-microbiome-may-affect-some-immune-responses-flu-vaccination

[1337] Hagan T, et al. *Cell.* 2019 Sep 5;178(6):1313-1328.e13. PMID: 31491384.

[1338] https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html

[1339] Haddock E, et al. *Proc Natl Acad Sci U S A.* 2021 Jan 12;118(2):e2015657118. PMID: 33443221.

[1340] https://www.niaid.nih.gov/news-events/reston-ebolavirus-spreads-efficiently-pigs

Nearly 250,000 people have received the investigational VSV-EBOV vaccine since August 2018 as part of a "ring vaccination" program to help stem the outbreak in the DRC.[1341] In FY 2019, NIH investigators showed that a single dose of highly diluted VSV-EBOV vaccine—approximately one-millionth of the dose being used in DRC—remains fully protective against disease in experimentally infected monkeys.[1342] The NIH investigators completed the vaccine dosage study using cynomolgus macaques and an updated vaccine component to match the Ebolavirus Makona strain that circulated in West Africa from 2014–16. These studies are important because of the continued need to vaccinate individuals in the DRC and surrounding countries, making a potential shortage of VSV-EBOV vaccine a real concern. Dose adjustment is a realistic solution to help ease the burden on vaccine development.

In addition to Ebolavirus vaccine development, NIH conducts and supports research to develop treatments for EVD. NIAID scientists, in collaboration with scientists in the DRC, isolated a monoclonal antibody (mAb114) from a survivor of the 1995 Ebola epidemic, and determined that in the DRC mAb114 prevented the virus from entering and infecting cells. The antibody mAb114 has since been developed, manufactured, and licensed for clinical studies to treat EVD. According to results from a clinical trial conducted in the DRC, mAb114 offers patients a greater chance of surviving EVD compared with another NIH-developed investigational treatment, ZMapp.[1343,1344] This study also shows that early diagnosis and treatment are associated with an increased likelihood of survival from EVD. The FDA approved mAb114 on December 21, 2020, under the marketing name Ebanga.

NIAID scientists and collaborators used a non-human primate model to study the preclinical efficacy of monoclonal antibody-based Ebola virus treatments.[1345] Results showed that after treatment with monoclonal antibodies, Ebola virus remained in the brain, which is naturally less subject to immune responses than most other areas of the body, causing disease recurrence. Understanding Ebola virus persistence after treatment has important implications for the long-term follow-up care of human survivors of EVD.

Many EVD survivors suffer from chronic, long-term health problems caused by Ebola, including headaches, joint pain, and eye problems. In a study of survivors of EVD in Liberia, researchers found that patients who had previously had EVD had a higher prevalence of certain health issues including uveitis (eye redness and pain), as well as abdominal, chest, neurologic, and musculoskeletal abnormalities upon physical exam, when compared with a control group of household and community contacts who did not have a history of EVD.[1346] However, even participants in the control group experienced a relatively high burden of health issues overall. The study began in 2015 and followed participants for five years. These findings, published

[1341] https://www.niaid.nih.gov/news-events/candidate-ebola-vaccine-still-effective-when-highly-diluted-macaque-study-finds
[1342] Marzi A, et al. *EBioMedicine*. 2019 Nov;49:223-231. PMID: 31631035.
[1343] https://www.niaid.nih.gov/news-events/investigational-drugs-reduce-risk-death-Ebola-virus-disease
[1344] Mulangu S, et al. *N Engl J Med*. 2019 Dec 12;381(24):2293-2303. PMID: 31774950.
[1345] Liu J, et al. *Sci Transl Med*. 2022 Feb 9;14(631):eabi5229. PMID: 35138912.
[1346] https://www.niaid.nih.gov/news-events/study-finds-ebola-survivors-liberia-face-ongoing-health-issues

in FY 2019, are from the first year of the study.[1347] Scientists do not yet fully understand what causes these after-effects, but NIH is working to better understand them.

Zika

Like its flavivirus relatives, Zika virus is primarily transmitted to humans through the bite of infected *Aedes aegypti* mosquitoes. Zika virus can be transmitted from an infected pregnant woman to her baby during pregnancy and can result in serious birth defects, including microcephaly.[1348] Less commonly, the virus can also be spread through intercourse or blood transfusion. Most people who become infected with Zika virus do not become sick. For the 20 percent of people who do develop symptoms, the illness is generally mild, and includes fever, rash, joint pain, and conjunctivitis (red eyes). Illness lasts several days to a week. In non-pregnant people, the virus is generally eliminated from the body after a few weeks, although it may remain longer in semen.[1349] In FY 2019–2021, NIH researchers developed potential vaccines and treatments to treat Zika viral infection and conducted studies to better understand how immunity to other infectious diseases might relate to Zika infection. NIAID scientists developed an experimental Zika vaccine that was evaluated in a phase 2 human clinical trial.

Ideally, to prevent congenital Zika syndrome, a Zika vaccine would be given to adolescents and adults of childbearing age before pregnancy. An experimental Zika vaccine lowered levels of virus in pregnant monkeys and improved fetal outcomes in a rhesus macaque model of congenital Zika virus infection.[1350] NIAID scientists developed the experimental vaccine and are currently evaluating it in a phase 2 human clinical trial. The vaccine uses a small, circular piece of DNA, or plasmid, containing genes that encode Zika virus surface proteins to induce an immune response.[1351] The study suggests that sterilizing immunity—an immune response that prevents infection entirely, with no detectable virus—may not be required for significant protection against congenital Zika syndrome.

Researchers from NCATS and NINDS used a variety of advanced drug screening techniques to test more than 10,000 compounds in search of a cure for Zika infection.[1352] They found that the widely used antibiotic methacycline, the most potent tetracycline, was effective in mice at preventing brain infections and reducing neurological problems associated with the virus.[1353] In addition, they found that drugs originally designed to combat Alzheimer's disease and brain inflammation may also help fight infections. In mouse models, methacycline reduced the amount of Zika virus present in the brain and mitigated neurological damage caused by Zika virus. Because tetracycline antibiotics have already been approved by FDA, these drugs could be quickly translated to the clinic and deployed in the treatment of the

[1347] PREVAIL III Study Group, et al. *N Engl J Med.* 2019 Mar 7;380(10):924-934. PMID: 30855742.
[1348] https://www.cdc.gov/zika/about/index.html
[1349] https://www.cdc.gov/pregnancy/zika/testing-follow-up/exposure-testing-risks.html
[1350] https://www.niaid.nih.gov/news-events/nih-developed-zika-vaccine-improves-fetal-outcomes-animal-model
[1351] Van Rompay KKA, et al. *Sci Transl Med.* 2019 Dec 18;11(523):eaay2736. PMID: 31852797.
[1352] https://ncats.nih.gov/news/releases/2020/commonly-used-antibiotic-shows-promise-for-combating-zika-infections
[1353] Abrams RPM, et al. *Proc Natl Acad Sci U S A.* 2020 Dec 8;117(49):31365-31375. PMID: 33229545

neurological complications of Zika virus. These common antibiotics also have the potential to be used as prophylactics when traveling to regions where Zika virus is endemic.

Another flavivirus spread by *A. aegypti* mosquitoes, dengue virus, infects about 50 million people each year, with 22,000 deaths, mostly in children.[1354] Researchers studied the 2016 epidemic of Zika in a longstanding cohort of children in Managua, noticing that many of them had dengue infection histories.[1355] In statistical models adjusted for sex and age, researchers discovered that children with a previous dengue virus infection before March 2015 had a significantly lower risk of symptomatic Zika virus infection. However, prior dengue virus infections did not affect the rate of total Zika virus infections, including both symptomatic and clinically inapparent cases. These data indicate that prior dengue immunity in children may be protective against symptomatic Zika infection.

A mosquito protein may provide insights into how to develop therapeutics against viruses like Zika and other flaviviruses. In FY 2021, researchers showed that the mosquito protein AEG12 strongly inhibits flaviviruses and weakly inhibits coronaviruses by destabilizing the viral envelope and breaking its protective covering.[1356] Mosquitoes produce AEG12 when they take a blood meal or become infected with flaviviruses.[1357] Like humans, mosquitoes mount a vigorous immune response against these viruses. The findings could lead to preventive agents or therapeutics against this class of viruses, which affect millions of people around the world.

Antimicrobial Resistance

Antimicrobial resistance is an NIH priority. This is a potentially deadly situation in which bacteria, fungi, and other microbes become resistant to most or all antimicrobial drugs. Antimicrobial resistance and *Clostridioides difficile*, a pathogen associated with the overuse of antibiotics, lead to more than three million infections and 48,000 deaths in the U.S. each year.[1358] Scientists across NIH are working to better understand how microbes develop resistance, to develop new diagnostics that can more quickly detect resistance, and to identify new antimicrobial drugs and vaccines to prevent and treat infections.

Gonorrhea is the second most commonly reported notifiable disease in the U.S. and the bacterium that causes gonorrhea, *Neisseria gonorrhoeae,* has progressively developed resistance to each of the antibiotics used to treat it, necessitating new treatment options.[1359] An investigational oral antibiotic called zoliflodacin was tested in a phase 2 multicenter clinical trial.[1360] It was found to be well-tolerated by patients, and it successfully cured most cases of uncomplicated gonorrhea. Zoliflodacin is a new type of oral antibiotic that inhibits DNA synthesis differently from those antibiotics with current FDA approval, and it has been awarded fast-track status by FDA for development as oral treatment for gonococcal

[1354] https://www.niaid.nih.gov/diseases-conditions/dengue-fever
[1355] Gordon A, et al. *PLoS Med*. 2019 Jan 22;16(1):e1002726. PMID: 30668565.
[1356] Foo ACY, et al. *Proc Natl Acad Sci U S A*. 2021 Mar 16;118(11):e2019251118PMID: 33688047
[1357] https://www.niehs.nih.gov/news/newsroom/releases/2021/march10/index.cfm
[1358] https://www.cdc.gov/drugresistance/biggest-threats.html
[1359] https://www.nih.gov/news-events/news-releases/novel-antibiotic-shows-promise-treatment-uncomplicated-gonorrhea
[1360] Taylor SN, et al. *N Engl J Med.* 2018 Nov 8;379(19):1835-1845. PMID: 30403954.

infections. Recruitment for phase 3 testing in the Netherlands, South Africa, Thailand, and U.S. began in FY 2019.[1361]

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[1362] The most common probiotics are made up of bacteria that belong to groups called *Lactobacillus* and *Bifidobacterium*. Other bacteria and yeast fungi may also be used as probiotics, such as *Saccharomyces boulardii*. Probiotics have shown promise for a variety of health purposes, including the prevention of sepsis.

In FY 2019, NIH scientists and their Thai colleagues showed that "good" bacteria, *Bacillus subtilus*, commonly found in probiotic digestive supplements, helps eliminate *Staphylococcus aureus*, a type of bacteria that can cause serious antibiotic-resistant infections.[1363] The scientists found that *B. subtilus* eliminated *S. aureus* in the guts of mice and prevented *S. aureus* from growing in the gut and nose of healthy individuals.[1364] Scientists plan to test if probiotic supplements containing only *B. subtilis* can eliminate *S. aureus* in humans.

Using viruses instead of antibiotics to treat drug-resistant bacteria is a promising strategy, known as bacteriophage or "phage therapy." NIAID scientists used two different bacteriophage viruses, individually and then together, to successfully treat research mice infected with multidrug-resistant *Klebsiella pneumoniae* sequence type 258 (ST258).[1365] *K. pneumoniae* ST258 is included on a CDC list[1366] of greatest antibiotic resistance threats in the U.S. and is associated with high rates of morbidity and mortality if infection is left untreated.[1367]

Infectious diseases that can be treated effectively with antibiotics yet recur frequently in some populations are of concern for developing antimicrobial resistance. For this reason, NIH scientists are studying approaches to better understand the biology of these infections.

Strep throat, caused by *Streptococcus pyogenes*, can be treated effectively with antibiotics, but some children get the disease repeatedly (recurrent tonsillitis).[1368] To gain a better understanding of recurrent tonsillitis, researchers acquired tissue samples of tonsils from children who had them removed due to recurrent tonsillitis and from children who had them removed for other medical reasons, such as sleep apnea.[1369] In the tonsils of children with recurrent tonsillitis, investigators found an unusual population of T cells, which appear to kill B cells that could prevent future recurrences.[1370] The team was also able to

[1361] https://www.clinicaltrials.gov/ct2/show/NCT03959527
[1362] Hill C, et al. Nat Rev Gastroenterol Hepatol. 2014 Aug;11(8):506-14. PMID: 24912386.
[1363] https://www.nih.gov/news-events/news-releases/nih-study-finds-probiotic-bacillus-eliminates-staphylococcus-bacteria
[1364] Piewngam P, et al. *Nature*. 2018 Oct;562(7728):532-537. PMID: 30305736.
[1365] Hesse S, et al. *mBio*. 2021 Feb 23;12(1):e00034-21. PMID: 33622728.
[1366] https://www.cdc.gov/hai/organisms/cre/
[1367] https://www.niaid.nih.gov/news-events/mouse-study-shows-bacteriophage-therapy-could-fight-drug-resistant-klebsiella
[1368] https://www.nih.gov/news-events/nih-research-matters/understanding-recurrent-tonsillitis
[1369] https://www.nih.gov/news-events/nih-research-matters/understanding-recurrent-tonsillitis
[1370] Dan JM, et al. *Sci Transl Med.* 2019 Feb 6;11(478):eaau3776. PMID: 30728285.

identify specific genetic variations in the immune system that were associated with risk of recurrent tonsillitis. These findings point to potential strategies to reduce the incidence of recurrent strep throat.

Salmonella bacteria live inside the gut, commonly causing human gastroenteritis by infecting the epithelial cells that line the surface of the intestine and cause inflammation. These bacteria cause about 1.35 million infections, 26,500 hospitalizations, and 420 deaths in the U.S. every year.[1371] Antibiotics are typically used only to treat people who have severe illness or who are at risk for it. In FY 2021, CDC published a study showing a rise in antimicrobial-resistant *Salmonella* infections.

NIAID scientists studying how *Salmonella* establish and maintain a foothold in the gastrointestinal tract of mammals, discovered that any attempts by the immune system to eliminate the bacteria from the gastrointestinal tract instead facilitates colonization of the epithelial cells in the intestinal tract the bacteria and fecal shedding of the bacteria.[1372,1373] These new insights offer new avenues for developing novel interventions to reduce the burden of this important pathogen.

Many studies have shown that *Salmonella* use a "run-and-tumble" method of swimming for a short period of time (runs) punctuated by tumbles where they randomly change direction, but how they move within the gut is not well understood.[1374] NIAID scientists and their colleagues identified a distinct subgroup within the *Salmonella enterica* species, called serovar Typhimurium (*S. typhimurium*), which produces a specific protein called McpC (methyl-accepting chemotaxis protein C). McpC allows the bacteria to swim straight when they are ready to infect cells.[1375] The study describes *S. typhimurium* movement and shows that McpC is required for the bacteria to invade surface epithelial cells in the gut, thus McpC may be a potential target for developing new antibacterial treatments against *Salmonella*.

COVID-19

Coronavirus disease 2019 (COVID-19) is caused by a newly discovered virus—the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus spreads easily from person to person through respiratory droplets, and infection typically causes fever, loss of taste or smell, shortness of breath, a dry cough, gastrointestinal symptoms, as well as other symptoms and complications. The ease with which the virus spreads and its ability to be transmitted by asymptomatic individuals has caused what is possibly the most severe worldwide infectious disease pandemic of the modern age. The COVID-19 pandemic was the third leading cause of death in the U.S. in 2021, resulting in approximately 460,000 deaths.[1376]

[1371] https://www.cdc.gov/salmonella/index.html

[1372] https://www.niaid.nih.gov/news-events/nih-scientists-find-salmonella-use-intestinal-epithelial-cells-colonize-gut

[1373] Chong A, et al. *Cell Host Microbe.* 2021 Jul 14;29(7):1177-1185.e6. PMID: 34043959.

[1374] https://www.niaid.nih.gov/news-events/nih-scientists-study-salmonella-swimming-behavior-clues-infection

[1375] Cooper KG, et al. *Nat Commun.* 2021 Jan 13;12(1):348. PMID: 33441540.

[1376] Provisional Mortality Data — United States, 2021, MMWR Morb Mortal Wkly Rep 2022;71:597-600. https://www.cdc.gov/mmwr/volumes/71/wr/mm7117e1.htm

NIH continues to lead a swift, coordinated research response[1377] to this public health crisis, outlined in the *NIH-Wide Strategic Plan for COVID-19 Research.*[1378] By leveraging existing funding mechanisms and establishing new programs, NIH has rapidly mobilized the disbursement of new emergency government funding to the biomedical research community while still maintaining a scientifically and ethically rigorous review process and strong scientific stewardship to support the most promising and meritorious science in view of this public health emergency.

Fundamental Knowledge

During FY 2019–2021, NIH conducted and supported research to better understand the biology of SARS-CoV-2 infection, acute COVID-19, and the post-acute sequalae of SARS-CoV-2 infection (PASC or long-COVID), as well as the impact that the infection and disease have on individuals, communities, and public health. As fundamental knowledge of SARS-CoV-2 and COVID-19 has grown over the past three years, it has been used to identify novel approaches and improvements to existing diagnostics, prevention strategies, and treatments. Importantly, it will also be leveraged to better prepare for future infectious disease outbreaks.

Fundamental Research

As soon as SARS-CoV-2 was discovered and sequenced, NIH-supported researchers were able to start building on an already strong foundation of viral infectious disease knowledge to understand SARS-CoV-2 infection and COVID-19.

A major part of being able to combat an infectious disease is understanding the infectious agent that causes the disease. Based on years of basic research, a team of NIAID researchers and collaborators developed the first atomic-scale map of the spike protein of SARS-CoV-2.[1379,1380] The spike protein allows the virus to bind to a receptor on human cells, which leads to a fusion of the viral and human cell membranes and subsequent entry of the virus into cells to infect them. This map of the spike protein was critical to the swift development of five of the USG-supported COVID-19 vaccines and all of the COVID-19 vaccines currently FDA approved and/or authorized in the U.S.

While the initial infection of a virus into a host is certainly an important step in the viral lifecycle, once inside the cell, the virus must replicate to survive. This is where the nucleocapsid protein, or N protein, comes into play. The N protein is the most abundant protein of SARS-CoV-2. It functions to package the viral genome into structures called ribonucleoprotein particles, which are then loaded into newly made virions that are released from an infected cell to infect surrounding cells. Due to its essential role in viral assembly and replication, the N protein is a promising immunological target to combat SARS-CoV-2 infection and prevent COVID-19.[1381]

[1377] https://covid19.nih.gov/nih-strategic-response-covid-19

[1378] *NIH-Wide Strategic Plan for COVID-19 Research*. https://covid19.nih.gov/sites/default/files/2021-05/NIH-Wide-COVID-19-StratPlan_2021_508_1.pdf

[1379] https://directorsblog.nih.gov/2020/03/03/structural-biology-points-way-to-coronavirus-vaccine/

[1380] Wrapp D, et al. *Science*. 2020 Mar 13;367(6483):1260-1263. PMID: 32075877; PMCID: PMC7164637.

[1381] Bai Z, et al. *Viruses*. 2021 Jun 10;13(6):1115. PMID: 34200602.

NIBIB researchers investigated how the N protein interacts with oligonucleotides (short stretches of DNA and RNA)—to demystify how the viral genome is packaged. Using biophysical methods, researchers found that when the N protein interacts with nucleotides of sufficient length, it adopts a shape that promotes interactions with other proteins. When the N protein binds with multiple copies of itself and long stretches of oligonucleotides, it can condense into highly concentrated droplets that are thought to ultimately enable the formation of ribonucleoprotein particles.[1382] So, targeting interactions between the N protein and its binding partners might be a viable way to inhibit the viral replication of SARS-CoV-2.

Researchers found that vitamin D and its metabolites can inhibit SARS-CoV-2 replication by interfering with critical viral functions, such as protein processing and RNA replication.[1383] There have been multiple reports since the early period of the COVID-19 pandemic that vitamin D has an antiviral effect, but this study was the first to demonstrate a potential mechanism for this effect. The findings suggest a potential new approach to target SARS-CoV-2. This is an example of how basic research in one area, in this case to better understand vitamin D metabolism in the skin, can be applied to a seemingly unrelated public health disease.

Virus-host interactions determine how infectious diseases spread through populations and can force the virus to evolve. Genomic sequencing and advanced computational modeling helped researchers across NIH and NIH-supported institutions better understand the patterns of SARS-CoV-2 transmission dynamics, variant emergence, and the evolutionary history of SARS-CoV-2.

Using a highly specialized strategy to compare SARS-CoV-1 (the coronavirus that caused the SARS outbreak of 2003 and occasionally re-emerges) and SARS-CoV-2, NLM researchers learned that specific ion channels, which play a role in virion assembly and release from cells, are conserved across many different coronaviruses.[1384] Their results suggest that proteins that are conserved across different coronaviruses are under varying levels of evolutionary pressure, which further suggests that the proteins that interface with the host during infection and/or immune attack by the host might be under pressure to evolve more quickly.[1385] This is helpful to better understand how SARS-CoV-2 may evolve and to develop mitigation strategies that can respond to virus evolution.

A group of FIC researchers analyzed samples collected in the Washington, D.C. metro region during March 2020, which comprised almost 30 percent of the total COVID-19 cases in Maryland and Washington, D.C..[1386] The researchers demonstrated that the diversity of the virus in this region rivaled global SARS-CoV-2 genetic diversity at that time, and that the identified sequences were representative of all of the major COVID-19 lineages then circulating globally, suggesting that there were multiple introductions of the virus into this geographic region. They concluded that efforts to control local spread of the virus were

[1382] https://www.nibib.nih.gov/news-events/newsroom/biophysical-study-sheds-light-potentially-druggable-process-sars-cov-2-replication
[1383] Qayyum S, et al. *Am J Physiol Endocrinol Metab*. 2021 Aug 1;321(2):E246-E251. PMID: 34181461.
[1384] Tan Y, et al. *bioRxiv*. 2020 Nov 11;2020.11.10.377366. PMID: 33200132.
[1385] Tan Y, et al. *Virus Evol*. 2021 Feb 16;7(1):veab014. PMID: 33692906.
[1386] Thielen PM, et al. *JCI Insight.* 2021 Mar 22;6(6):e144350. PMID: 33749660.

likely confounded by the number of introductions in the geographic region early in the pandemic and the interconnectedness of this geographic region as a whole.

NLM researchers have also identified two pathways of evolution for SARS-CoV-2 and determined that there have been four distinct periods of the pandemic to date, each characterized by a unique virus mutation.[1387] The results show that the ongoing evolution of SARS-CoV-2 during the pandemic has been characterized primarily by purifying selection, which hinders the spread of variants that are not beneficial for viral transmission. However, a small set of sites appear to evolve under positive selection, which promotes the spread of variants beneficial to viral transmission. While virus diversity within each geographic region has been steadily growing during the pandemic, analyses across geographic regions support the four-period theory, based on the emergence of key mutations.

Preclinical Models

Animal models, particularly those that replicate human disease, are essential to better understanding the basic biology of coronaviruses, including transmission, incubation periods, and host immune responses to infection. These models are also critical to testing potential preventive and therapeutic strategies.

NIH researchers across the entirety of the biomedical and behavioral research portfolio found ways to pivot their research to be applicable to SARS-CoV-2 and COVID-19. For example, NIAMS intramural researchers were already designing "nanobodies" to protect people from acquisition of HIV infection. Nanobodies, which are similar to the antibodies humans produce in response to most infections, also occur naturally in some mammal species, such as camels, llamas, and alpacas. The researchers applied their knowledge and approach to SARS-CoV-2 and generated nanobodies from mice and llamas that are highly specific to the SARS-CoV-2 spike protein.[1388] They are continuing to explore whether monoclonal nanobodies, derived from specially modified mice or llamas, could be developed into a prophylactic treatment to prevent COVID-19 in humans.

[1387] Rochman ND, et al. *Proc Natl Acad Sci U S A*. 2021 Jul 20;118(29):e2104241118. PMID: 34292871.
[1388] Xu J, et al. *Nature.* 2021 Jul;595(7866):278-282. PMID: 34098567.

Figure 32: Llamas make nanobodies that may serve as the basis for potential COVID-19 therapies. Credit: Jianliang Xu (NIAMS) and Capralogics

A team of scientists from NCATS and the United States Naval Research Laboratory developed a new tool that mimics how SARS-CoV-2 infects a cell, providing information that could potentially speed the search for treatments against the disease.[1389] The tool is a fluorescent nanoparticle probe that uses the spike protein on the surface of SARS-CoV-2 to bind to cells and trigger the process that pulls the virus into the cell.[1390] The probe could be used in tests to rapidly gauge the ability of biologics, drugs, and compounds to block the actual virus from infecting human cells.

NIH is also developing and validating human microphysiological systems, tissue chips or engineered 3D platforms that support living human cells and tissues, which can be used to study viral infections in relevant human tissue models and in more clinically predictive assay systems to test new treatments. Systems biology and computational techniques are being used to complement preclinical models and aid in the evaluation of therapeutic effects against SARS-CoV-2 and COVID-19.

Tissue chip devices are designed as accurate models of the structure and function of human organs, such as the lungs, liver, and heart. NCATS was able to quickly distribute additional funding to tissue chip investigators who proposed applying their work to pressing COVID-19 concerns.[1391] Investigators suggested projects to evaluate the properties of SARS-CoV-2, the mechanisms of COVID-19 disease pathology, potential COVID-19 therapeutics of known action, as well as the potential repurposing of

[1389] https://ncats.nih.gov/news/releases/2020/ncats-nrl-create-nanoparticle-sars-cov-2-model-to-speed-drug-discovery-for-covid-19
[1390] Gorshkov K, et al. *ACS Nano.* 2020 Sep 22;14(9):12234-12247. PMID: 32845122.
[1391] https://ncats.nih.gov/tissuechip/projects/covid19

approved drugs for use against COVID-19. One of the funded tissue chip projects identified the SARS-CoV-2-inhibiting effects of the antimalarial drug amodiaquine, which are being tested in clinical trials as an option against COVID-19 in low-resource nations where access to vaccines and expensive new therapeutics is limited.[1392]

Computer-aided virtual screening is commonly used to analyze large collections of existing compounds to identify those that have the potential to be useful drugs. NCATS developed a new biological activity-based modeling (BABM) approach in which compound activity profiles established across multiple assays are used as signatures to predict compound activity in other assays or against a new target.[1393] With BABM, scientists do not need to know the compound's structure. Rather, they use measurements of a compound's biological activity patterns to predict whether it will be effective against the new target. BABM can quickly scan thousands of drugs to help identify new potential treatments for diseases such as COVID-19. BABM models were applied to identify ~100 compounds that showed activity against SARS-CoV-2 in a live virus assay. The most potent of these compounds have the potential to be further developed into anti-SARS-CoV-2 therapies. The general concept of BABM can be extended to any type of biological data and shows the promise of broad applications in different areas of biology.

Population Dynamics and Surveillance

Gaps exist in understanding the dynamics of SARS-CoV-2 transmission in different populations over time and the factors that influence a population's susceptibility to severe disease. Researchers continue to work toward understanding the progression of SARS-CoV-2 infection through natural history studies. These studies may reveal why some groups, such as older adults and people with preexisting conditions, are at higher risk of severe COVID-19 than others.

In FY 2020, a group of scientists discovered genetic and immunologic underpinnings of some cases of severe COVID-19.[1394] The scientists found that more than ten percent of people who develop severe COVID-19 have misguided antibodies that attack their own immune system rather than SARS-CoV-2.[1395] Another 3.5 percent or more of people who develop severe COVID-19 carry a specific kind of genetic mutation that impacts immunity.[1396] Consequently, both groups are unable to mount an immune response driven by type I interferons, which are crucial for protecting cells and the body from viruses. Whether these proteins have been neutralized by those autoantibodies or—because of a faulty gene—were produced in insufficient amounts or induced an inadequate antiviral response, their absence appears to be a commonality among a subgroup of people who suffer from life-threatening COVID-19 pneumonia.

The Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC), an NIAID-supported study, is tracking the immune responses of 1,000 people who were hospitalized with COVID-19 at ten research

[1392] https://wyss.harvard.edu/news/human-organ-chips-enable-rapid-drug-repurposing-for-covid-19/
[1393] Huang R, et al. *Nat Biotechnol.* 2021 Jun;39(6):747-753. PMID: 33623157.
[1394] https://www.niaid.nih.gov/news-events/scientists-discover-genetic-and-immunologic-underpinnings-some-cases-severe-covid-19
[1395] Bastard P, et al. *Science.* 2020 Oct 23;370(6515):eabd4585. PMID: 32972996.
[1396] Zhang Q, et al. *Science*. 2020 Oct 23;370(6515):eabd4570. PMID: 32972995.

sites across the U.S.[1397] IMPACC has brought together researchers from multiple consortiums and research groups, all with a common goal: to determine how certain immunological measures correspond to, or may even predict, the clinical severity of COVID-19.[1398] Participants are followed for up to 12 months after their hospitalization to assess how well they recover and whether they develop durable immunity to the virus. Data collected in the IMPACC study will help inform recommendations for COVID-19 care and identify new targets and optimal timing for experimental treatments.

Pandemic preparedness requires that innovative surveillance mechanisms be created for early detection of new, potentially dangerous infectious pathogens. NLM researchers contributed to the development of advanced computational methods, which they applied to waste-water pathogen surveillance[1399] and surveillance of viral recombination[1400] to predict how new SARS-CoV-2 infections may emerge. These efforts will help to inform and predict coronavirus genome recombination and could provide insights into the prevention and prediction of future coronavirus or other infectious disease outbreaks.

The ability to monitor respiratory conditions and symptoms, such as coughing frequency, can provide essential information to patients and health care providers for managing their illness and care. A new device developed to monitor asthma symptoms[1401] is now being repurposed and tested for possible use in monitoring the symptoms of patients with COVID-19. The device can be worn as a flexible patch on the upper body. Conceptualized by an NINR-supported nurse scientist, and now patented and licensed by the grantee to a digital health company, the device has been cited by an industry publication as one of the top wearable technologies in 2020.

Short- and Long-Term Health Consequences

During FY 2019–2021, as more and more information started to emerge on the short- and long-term effects of SARS-CoV-2 infection, NIH mapped out a strategic response to better understand these health consequences—especially how they differ across the life course—and learn how best to address them.

NIH is supporting research to better understand and address the impacts of the virus and public health measures used to prevent its further spread. NICHD is conducting and supporting a number of studies to understand the direct and indirect health consequences of the COVID-19 pandemic on child development. One study found that between 37,300 and 43,000 children have lost a parent to COVID-19.[1402] In FY 2021, NICHD started assessing the impact of pandemic-related changes, including remote learning and wearing masks, on child development, through supplemental funding to two ongoing childhood studies, to understand mask usage and behaviors among children from geographically diverse areas.[1403] NICHD-

[1397] https://www.niaid.nih.gov/news-events/niaid-study-examines-immune-responses-people-covid-19
[1398] IMPACC Manuscript Writing Team; IMPACC Network Steering Committee. *Sci Immunol.* 2021 Aug 10;6(62):eabf3733. PMID: 34376480.
[1399] Fontenele RS, et al. *Water Res*. 2021 Oct 15;205:117710. PMID: 34607084.
[1400] Yang Y, et al. *Mol Biol Evol.* 2021 Apr 13;38(4):1241-1248. PMID: 33146390.
[1401] Rhee H, et al. *JMIR Mhealth Uhealth.* 2014 Jun 19;2(2):e27. PMID: 25100184.
[1402] Kidman R, et al. *JAMA Pediatr*. 2021 Jul 1;175(7):745-746. PMID: 33818598.
[1403] https://covid19.nih.gov/news-and-stories/how-does-wearing-masks-affect-children

supported researchers also demonstrated that American children may have adopted a range of behaviors that increase their risk for obesity in response to the COVID-19 pandemic.[1404]

Researchers are also investigating the long-term effects of SARS-CoV-2 infection, with or without acute COVID-19, as well as the influence of physical, environmental, neurobiological, social, and behavioral factors.

NIA-funded research is underway to evaluate the neurological and neurocognitive PASC in aging populations. This study has found that COVID-19 induces brain inflammation and dysregulation in those infected with SARS-CoV-2.[1405] Although researchers did not find evidence of SARS-CoV-2 inside the brain, the virus-induced inflammation appears to be relayed into the brain, triggering dysregulation that mirrors that of chronic brain disorders, such as depression and schizophrenia. In addition, related research suggests that neurological disorders may result from SARS-CoV-2 infection. In a prospective study of nearly 4,500 hospitalized COVID-19 patients in New York City, 13.5 percent developed a neurological disorder coincident with SARS-CoV-2 infection.[1406] Common neurological diagnoses included toxic/metabolic encephalopathy, stroke, seizure, and hypoxic/ischemic injury. Those who developed neurological disorders were more often older, male, White, hypertensive, diabetic, intubated, and experiencing multiple organ failure. Having a neurologic disorder also predicted lesser likelihood of discharge and greater likelihood of in-hospital death.

During FY 2019–2021, a striking relationship emerged between infectious disease outbreaks and increased wildfires. Exposure to wildfire smoke can increase the risk of lung infections, including SARS-CoV-2. According to NIEHS-funded research, thousands of COVID-19 cases and deaths in 92 counties in the western U.S. may be attributable to increases in fine particulate matter air pollution (PM2.5) from wildfires.[1407] Researchers developed a model to estimate the association between daily changes in PM2.5 and the percentage increase in COVID-19 cases and deaths, up to 28 days after exposure. From August to October 2020, when fire activity was greatest, daily levels of PM2.5 during wildfire days were significantly higher than on non-wildfire days.[1408] The total numbers of COVID-19 cases and deaths attributable to daily increases in PM2.5 from wildfires were 19,742 and 748, respectively.

NIH is committed to conducting and supporting research to address the challenges that the COVID-19 pandemic poses to the Nation's mental health. These include studies that aim to examine community and digital health interventions that address new or worsening mental health problems, and those to help learn how the shift to telehealth might impact mental health care. NIMH-funded researchers recently identified childhood risk factors such as behavioral inhibition, a temperament characterized by fearful or

[1404] https://www.nichd.nih.gov/newsroom/news/083121-COVID-19-impact
[1405] Yang AC, et al. *Nature*. 2021 Jul;595(7868):565-571. Erratum in: Nature. 2021 Oct;598(7882):E4. PMID: 34153974.
[1406] Frontera JA, et al. *Neurology.* 2021 Jan 26;96(4):e575-e586. PMID: 33020166.
[1407] https://factor.niehs.nih.gov/2021/10/papers/dert/index.htm#a4
[1408] Zhou X, et al. *Sci Adv.* 2021 Aug 13;7(33):eabi8789. PMID: 34389545.

avoidant responses toward unfamiliar people and situations, which predicted heightened anxiety in young adults during the COVID-19 pandemic.[1409,1410]

In another study, the *All of Us* Research Program deployed a new online survey to better understand the effects of the COVID-19 pandemic on participants' physical and mental health.[1411] The COVID-19 Participant Experience (COPE) Survey was a 20- to 30-minute survey designed both for participants who have been ill with COVID-19, and those who have not. It included questions on COVID-19 symptoms, stress, social distancing, and economic impacts. Participants were invited to take the survey several times, so researchers can study the effects of COVID-19 over time and better understand how and why COVID-19 affects people differently.

NIH studies are also exploring the health consequences from delayed care during the pandemic, not only for COVID-19, but also for routine preventive practices (such as vaccinations) and the detection and treatment of other diseases and conditions (such as cancer).

For the millions of people living with a rare disease, COVID-19 presents challenges ranging from potential reduced access to necessary medical care, to possible heightened anxiety and stress.[1412] An online survey launched by the NCATS-led Rare Diseases Clinical Research Network (RDCRN) aimed to determine how the COVID-19 pandemic is impacting individuals with rare diseases, their families, and their caregivers. The survey responses indicated that the pandemic negatively affected rare disease patients and their caregivers in terms of access to health care, special treatment, and hospitalization, even among those who reported acquiring SARS-CoV-2 infection.[1413] Some respondents had difficulty receiving treatments for their rare disease, especially those requiring special diets, occupational therapies, and physical therapies. The pandemic also caused mood changes, anxiety, and stress, in both the patients and their family members, to an extent that required medical attention.

In FY 2020, NIH launched the NCI COVID-19 in Cancer Patients Study,[1414] which is a natural history study to track cancer patients who also had COVID-19 to learn how COVID-19 and cancer impact one another and to gain knowledge for treatment management of patients with both diseases.[1415] This study is designed to characterize patient factors associated with long- and short-term outcomes of SARS-CoV-2 infection and COVID-19 in patients undergoing treatment, describe cancer treatment modifications made in response to COVID-19, create a biobank of patient samples and clinical characterization for future research use, and evaluate the associations of COVID-19 with cancer outcomes.

[1409] https://www.nimh.nih.gov/news/science-news/2021/study-identifies-risk-factors-for-elevated-anxiety-in-young-adults-during-covid-19-pandemic

[1410] Zeytinoglu S, et al. *J Am Acad Child Adolesc Psychiatry.* 2021 Oct;60(10):1300-1308. PMID: 33582223.

[1411] https://databrowser.researchallofus.org/survey/covid-19-participant-experience

[1412] https://ncats.nih.gov/news/releases/2020/nih-supported-research-survey-to-examine-impact-of-covid-19-on-rare-diseases-community

[1413] https://www.rarediseasesnetwork.org/news/2021-02-10-COVID19-survey-preliminary-results

[1414] https://www.cancer.gov/research/key-initiatives/covid-19/coronavirus-research-initiatives/nccaps

[1415] NCT04387656. https://clinicaltrials.gov/ct2/show/NCT04387656

The Cancer Intervention and Surveillance Network (CISNET) is a consortium of NCI-sponsored investigators who use simulation modeling to improve understanding of cancer control interventions and their effects on population trends in incidence and mortality.[1416] Conservative CISNET modeling of the effect of the COVID-19 pandemic on cancer screening and treatment for breast and colorectal cancers over the next decade suggests there will be almost 10,000 excess deaths from breast and colorectal cancer, which is an approximate one percent excess in deaths from these cancer types during this period.[1417]

During the pandemic, many hospitals encountered unprecedented caseloads of acutely ill patients with COVID-19, which caused an imbalance in the demand versus supply of space, supplies, and staff. Many surging hospitals resorted to desperate measures such as makeshift bed expansion. However, the downstream effects of the strain of hospital surges on patient outcomes remained unclear. NIH scientists, in collaboration with CDC, formulated a surge index that considers illness severity, hospital resources, and baseline bed capacity, in addition to patient counts, enabling comparison of surge strain and its impacts across hospitals.[1418] Among 140,000 patients with COVID-19 at 558 U.S. hospitals early in the pandemic, risk-adjusted odds of mortality nearly doubled at the highest surging hospitals, and one in four COVID-19 deaths was attributable to the strain of surges. This research raised awareness that many lives could be saved by simply avoiding hospitals from becoming critically overcrowded with COVID-19 patients. This message has been instrumental in bolstering regional and national efforts to enhance interhospital transfer capability and coordination. The findings also reinforce the importance of preventative public health measures (such as vaccination and masking) to avoid hospital COVID-19 caseload surges from occurring in the first place.

Detection

From FY 2019–FY 2021, a vital component of the *National Strategy for the COVID-19 Response and Pandemic Preparedness*[1419] has been standing up and then improving upon the ability to detect, diagnose, and survey the population to identify and quarantine COVID-19 cases and track the spread of the virus. NIH research made significant contributions to increase the number of tests available—both viral tests to indicate current infection and serological tests to indicate prior infection—and ensure their specificity and sensitivity as new SARS-CoV-2 variants emerged. In FY 2020, NIH launched the Rapid Acceleration of Diagnostics (RADx®) initiative to speed innovation in the development, commercialization, and implementation of technologies for SARS-CoV-2 testing. More information on RADx and its four programs can be found below in the Research Resources and Infrastructure subsection.[1420]

[1416] https://cisnet.cancer.gov/

[1417] Sharpless NE. *Science*. 2020 Jun 19;368(6497):1290. PMID: 32554570.

[1418] https://www.nih.gov/news-events/news-releases/nih-study-associates-covid-19-surges-mortality-increases-patients

[1419] *National Strategy for the COVID-19 Response and Pandemic Preparedness*. https://www.whitehouse.gov/wp-content/uploads/2021/01/National-Strategy-for-the-COVID-19-Response-and-Pandemic-Preparedness.pdf

[1420] https://www.nih.gov/research-training/medical-research-initiatives/radx

Diagnostic Technologies

Standard tests for detection of SARS-CoV-2 involve extracting viral RNA from samples of interest and amplifying viral RNA to detectable levels using a technique called quantitative reverse transcription polymerase chain reaction (RT-qPCR). Manufacturers of RNA extraction kits have had difficulty keeping up with demand during the COVID-19 pandemic, hindering testing capacity worldwide. As new virus variants emerged, so did the need for better, faster tests. In 2020, the NIH-funded COVID-19 home test was the first to receive over-the-counter authorization from FDA.[1421]

Scientists from CC, NEI, and NIDCR worked together to develop a faster, safer, and cheaper diagnostic test for SARS-CoV-2.[1422] Their new virus sample preparation method eliminated time-consuming steps of viral RNA extraction, while also increasing test sensitivity.[1423]

Serological Assays

Serological assays, or those that detect antibodies in the blood of individuals, have been critical to accounting for the spread of SARS-CoV-2 across the U.S. and globe, and to monitoring levels of immunity in the community due to natural infection and/or vaccination.

NIH researchers, including intramural research groups at NIAID, NCATS, NIBIB, and the Frederick National Laboratory for Cancer Research, collaborated to enable a serosurvey study to quantify undetected coronavirus cases. They reported that the prevalence of COVID-19 in the U.S. during the spring and summer of 2020 far exceeded the known number of cases and that infection affected the country unevenly.[1424] For every diagnosed COVID-19 case in this timeframe, the researchers estimate that there were 4.8 undiagnosed cases, representing an additional 16.8 million cases by July 2020 alone.[1425] The team's analysis of blood samples from people who did not have a previously diagnosed SARS-CoV-2 infection, along with socioeconomic, health, and demographic data, offers insight into the undetected spread of the virus and subgroup vulnerability to undiagnosed infection.

In June 2020, the *All of Us* Research Program[1426] announced that it was leveraging its significant and diverse participant base to seek new insights into COVID-19.[1427] Beyond the ongoing collection of electronic health record (EHR) information, the program launched an antibody testing study and a new survey on the pandemic's impacts. For example, *All of Us* tested more than 24,000 stored blood samples collected between January 2 and March 18, 2020, to look for SARS-CoV-2 antibodies, and found evidence

[1421] https://www.nih.gov/news-events/news-releases/nih-funded-covid-19-home-test-first-receive-over-counter-authorization-fda
[1422] https://www.nei.nih.gov/about/news-and-events/news/nih-scientists-develop-faster-covid-19-test
[1423] Guan B, et al. *iScience*. 2021 Sep 24;24(9):102960. PMID: 34396082.
[1424] https://www.nih.gov/news-events/news-releases/nih-study-suggests-covid-19-prevalence-far-exceeded-early-pandemic-cases
[1425] Kalish H, et al. *Sci Transl Med*. 2021 Jul 7;13(601):eabh3826. PMID: 34158410.
[1426] https://www.researchallofus.org/
[1427] https://allofus.nih.gov/news-events/announcements/all-us-research-program-launches-covid-19-research-initiatives

of SARS-CoV-2 infections in five U.S. states earlier than had initially been reported.[1428] The results expanded on findings from a CDC study that suggested SARS-CoV-2 was present in the U.S. as early as December 2019. These positive samples were collected prior to the first reported cases in Illinois, Massachusetts, Mississippi, Pennsylvania, and Wisconsin, demonstrating the importance of expanding testing as quickly as possible in disease outbreak settings.

The Serological Sciences Network (SeroNet) was established in 2020 to address the critical national need to better understand and support serology testing during the COVID-19 pandemic. SeroNet is the Nation's largest coordinated effort to study the immune response to SARS-CoV-2 infection and COVID-19, bringing together investigators across scientific disciplines from more than 25 organizations to conduct fundamental research on all aspects of the immune response to the virus, serological assay validation, and expanded national testing capacity. [1429] SeroNet research addresses urgent questions in the cancer community, where immunocompromised patients are at a higher risk for worse COVID-19 outcomes, such as understanding whether an individual is protected from COVID-19 following natural infection or vaccination, how long that immunity lasts, and whether or when a vaccine booster is needed. During SeroNet's first year, investigators published more than 100 peer-reviewed articles highlighting not only the urgency of the pandemic, but the power of scientific collaboration and the impact of research for the cancer community and the general public.

Accurate measurement of antibodies is critical to understanding how immunity develops, how strong it is, and how long it lasts, particularly in people with very mild or asymptomatic infection. Quantitative details about antibodies will also help researchers evaluate the effectiveness of vaccines. NIDCR and other NIH scientists adapted a method to detect antibodies in autoimmune disorders[1430] and applied it to the study of SARS-CoV-2. The adapted method detected antibodies specific to two SARS-CoV-2 proteins (the spike protein and the nucleocapsid protein) with very high sensitivity and specificity.[1431] This meant that the tests likely detected even trace amounts of antibodies in people with SARS-CoV-2 infection and were unlikely to falsely report the presence of antibodies in people without the infection.

Testing Implementation

Ensuring that newly developed and FDA-authorized tests for SARS-CoV-2 infection were effective and accessible to the public required—and continues to require—an all-of-government effort with NIH leading the continual evaluation of the sensitivity and specificity of tests to detect new variants of SARS-CoV-2.

One of four RADx programs, the RADx Underserved Populations (RADx-UP) Safe Return to School Diagnostic Testing Initiative, was awarded in FY 2021 (up to $33 million over two years) to fund projects at ten institutions across eight states to build evidence on safely returning students, teachers, and support

[1428] https://allofus.nih.gov/news-events/announcements/nih-study-offers-new-evidence-early-sars-cov-2-infections-us

[1429] https://www.cancer.gov/research/key-initiatives/covid-19/coronavirus-research-initiatives/serological-sciences-network

[1430] Burbelo PD, et al. *J Dent Res*. 2019 Jul;98(7):772-778. PMID: 31095438.

[1431] Burbelo PD, et al. *J Infect Dis*. 2020 Jun 29;222(2):206-213. PMID: 32427334.

staff to in-person school in areas with vulnerable and underserved populations.[1432] The institutions include public, tribal, special education, early childhood, and charter schools, accounting for more than 600,000 students and at least 75,000 staff, parents, and community members. The community-engaged projects will provide evidence for the effectiveness, sustainability, and scalability of COVID-19 testing approaches and mitigation strategies (e.g., masking, physical distancing, vaccination) in school settings. The studies will also help provide understanding of the social, behavioral, and ethical implications of implementation of SARS-CoV-2 testing within the identified communities. Recent findings showed that universal masking drastically reduced the spread of SARS-CoV-2 and that weekly COVID-19 saliva testing helped to reduce transmission in schools for children with disabilities.[1433]

Another program supported by RADx-UP, Say Yes! COVID Test (SYCT), which was launched in April 2021, explored how to best implement at-home testing in ten underserved U.S. communities.[1434] Nearly seven million SARS-CoV-2 tests were delivered to U.S. households. Analysis of the program and its significance in decreasing the spread of SARS-CoV-2 is ongoing. SYCT also shared best practices with the United States Digital Service (USDS) and United States Postal Service (USPS) distribution teams to reach underserved communities during the distribution of tests via the website covidtests.gov.

In real-world settings, changes in the number of reported COVID-19 cases can be difficult to interpret because of factors such as fluctuating testing levels or lags in reporting results. An NIH Common Fund Early Independence Awardee devised a new approach to accurately identify emerging COVID-19 hotspots.[1435] This new approach uses the amount of virus detected in positive SARS-CoV-2 diagnostic tests to determine when and where samples have particularly high levels of virus present, an indicator that a location is likely to be experiencing an outbreak.[1436]

Treatments

Normally, the discovery and development of a new therapeutic is a years-long process. The unprecedented need brought on by the COVID-19 pandemic has compelled a paradigm shift in the process that has enhanced the sharing of knowledge, resources, and infrastructure among academics, federal agencies, and industry. Through such a shift, NIH was able to expedite the selection and testing of interventions to treat COVID-19, while continuing to apply rigorous standards to ensure safety and efficacy. In April of 2020, NIH launched the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership to develop a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines.[1437] Coordinated by the Foundation for the National Institutes of Health, ACTIV brings NIH together with its sibling agencies in the Department of Health and Human Services (including BARDA, CDC, and FDA), other government agencies (including the DoD and Department of Veterans Affairs (VA)), Countermeasures Acceleration Group (formerly known

[1432] https://www.nih.gov/news-events/news-releases/nih-funded-covid-19-testing-initiative-aims-safely-return-children-person-school
[1433] https://www.nichd.nih.gov/newsroom/news/092021-COVID-testing-IDDs
[1434] https://sayyescovidhometest.org/
[1435] https://directorsblog.nih.gov/2021/06/24/new-metric-identifies-coronavirus-hotspots-in-real-time/
[1436] Hay JA, et al. *Science.* 2021 Jul 16;373(6552):eabh0635. PMID: 34083451.
[1437] https://www.nih.gov/research-training/medical-research-initiatives/activ

as Operation Warp Speed), the European Medicines Agency (EMA), along with representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies.

NIH has made great strides in treating COVID-19 in a short amount of time, and the chances of surviving this disease have significantly improved since the beginning of the pandemic. Much of this progress has been achieved by repurposing investigational treatments or those approved for other indications.

In October 2020, as part of the ACTIV-1 study,[1438] NCATS launched a phase 3 clinical trial to evaluate whether temporarily suppressing an overactive immune response can reduce the severity of COVID-19, shorten hospital stays, and—most important—save lives.[1439] The trial is testing three immune modulator drugs, two of which are currently FDA-approved for other indications and the third of which is in late-stage investigational development.[1440] The trial plans to enroll approximately 2,000 hospitalized adults with moderate to severe COVID-19 in the U.S. and Latin America. The CTSA Program and its Trial Innovation Network are playing key roles at more than 30 U.S. study sites to ensure that participants reflect the demographics of the country and the pandemic, which has disproportionately affected minority and rural communities.

NICHD intramural researchers found that the investigational oral drug TEMPOL impairs the activity of a key viral enzyme, thus limiting SARS-CoV-2 infection in cell culture experiments.[1441] The scientists discovered TEMPOL's potential as a COVID-19 treatment by evaluating a more basic question about how SARS-CoV-2 uses its RNA replicase, an enzyme that allows the virus to replicate its genome and make copies of itself once inside a human cell.[1442] The study team plans to conduct additional animal studies and will seek opportunities to evaluate TEMPOL in a clinical study of COVID-19.

NIA-funded research further showed that a class of drugs known as senolytics may protect against coronavirus in older animals. In this preclinical work, investigators sought to understand whether senescent cells, cells that have lost normal function as part of the aging process, contribute to COVID-19-related morbidity and mortality among older animals. Researchers found that senescent cells in older mice suppressed normal immune responses and heightened inflammation when exposed to a SARS-CoV-2-like virus.[1443] In addition, the activity of the senescent cells was associated with death in nearly 100 percent of the infected older mice, while 89 percent of the young mice survived. However, when older mice were treated with senolytic drugs, which eliminate or reduce senescent cells, researchers saw decreased inflammation, an improved immune response, and 50 percent increased survival. These findings suggest that senolytics may boost protection against SARS-CoV-2 infection especially for older patients, and clinical trials have begun to test this.

[1438] https://activ-1.org/

[1439] https://ncats.nih.gov/news/releases/2020/nih-begins-large-clinical-trial-to-test-immune-modulators-for-treatment-of-covid-19

[1440] NCT04593940. https://clinicaltrials.gov/ct2/show/NCT04593940

[1441] Maio N, et al. *Science.* 2021 Jul 9;373(6551):236-241. PMID: 34083449.

[1442] https://www.nichd.nih.gov/newsroom/news/060321-COVID-19-TEMPOL

[1443] Camell CD, et al. *Science.* 2021 Jul 16;373(6552):eabe4832. PMID: 34103349.

Remdesivir is an investigational broad-spectrum antiviral treatment originally developed to treat EVD, which has been shown to be effective against SARS-CoV-2 in several clinical trials. Early results from a clinical trial demonstrated that remdesivir is superior to the standard of care for the treatment of COVID-19.[1444] The Adaptive COVID-19 Treatment Trial (ACTT), sponsored by NIAID, enrolled hospitalized adults with COVID-19 with evidence of lower respiratory tract involvement (generally classified as moderate to severe disease). Investigators found that remdesivir was most beneficial for hospitalized patients with severe disease who required supplemental oxygen.[1445] In the second iteration of ACTT (ACTT-2), remdesivir was combined with baricitinib, an anti-inflammatory drug, and the combination reduced time to recovery for people hospitalized with COVID-19.[1446]

Through its CTSA Program, NCATS sponsored two randomized, placebo-controlled clinical trials to evaluate convalescent plasma as a treatment for patients hospitalized with COVID-19.[1447] Convalescent plasma treatment contains antibodies and other immune cells needed to fight the infection and requires transfusions of blood plasma donated by people who have recovered from COVID-19. Convalescent plasma did not meet the primary and secondary outcomes for clinical improvement in these two clinical trials.[1448] However, the Continuous Monitoring of Pooled International Trials of ConvaLEscent Plasma for COVID-19 Hospitalized Patients (COMPILE) project, which used pooled data from eight clinical trials, identified pre-existing health conditions and other clinical characteristics associated with the patients who most benefited from convalescent plasma treatment.[1449] Using this meta-analysis, the COMPILE project team developed a treatment benefit index that can be used prospectively to more precisely identify patients who may benefit from convalescent plasma therapy.

NCATS is overseeing a large, randomized, placebo-controlled phase 3 clinical trial to test several existing prescription and over-the-counter medications for people to self-administer to treat symptoms of COVID-19 through its CTSA program.[1450] Part of ACTIV, the ACTIV-6 trial aims to provide evidence-based treatment options for the majority of adult patients with COVID-19 who have mild-to-moderate symptoms and are not sick enough to be hospitalized.[1451] The ACTIV-6 protocol will explore a pool of up to seven drugs approved by FDA for other conditions—an approach called drug repurposing—and test their safety and effectiveness in treating mild-to-moderate COVID-19.[1452] Since the drugs under consideration already have been tested in humans, repurposing could deliver COVID-19 treatment options sooner. The trial will focus on enrollment of people within minority, rural, and other communities that are

[1444] https://www.niaid.nih.gov/news-events/peer-reviewed-data-shows-remdesivir-covid-19-improves-time-recovery
[1445] Beigel JH, et al. *N Engl J Med*. 2020 Nov 5;383(19):1813-1826. PMID: 32445440.
[1446] Kalil AC, et al. *N Engl J Med*. 2021 Mar 4;384(9):795-807. PMID: 33306283.
[1447] https://ncats.nih.gov/news/releases/2020/nih-expands-clinical-trials-to-test-convalescent-plasma-against-covid-19
[1448] Ortigoza MB, et al. *JAMA Intern Med.* 2022 Feb 1;182(2):115-126. PMID: 34901997.
[1449] Troxel AB, et al. *JAMA Netw Open*. 2022 Jan 4;5(1):e2147331. Erratum in: *JAMA Netw Open*. 2022 Mar 1;5(3):e224556. PMID: 35076699.
[1450] https://ncats.nih.gov/news/releases/2021/large-clinical-trial-to-study-repurposed-drugs-to-treat-covid-19-symptoms
[1451] https://activ6study.org/
[1452] https://clinicaltrials.gov/ct2/show/NCT04885530

significantly affected by COVID-19 but lack access to major academic medical centers, where large clinical trials usually take place.

Vaccines

To achieve COVID-19 pandemic control and prevent future outbreaks, it was imperative that safe and effective vaccines for SARS-CoV-2 be developed and distributed as quickly as possible. The NIH intramural program played an important role in the decades of basic research that led to the rapid and landmark design and development of the mRNA vaccines developed by NIH and Moderna (Spikevax)[1453] and Pfizer/BioNTech (Comirnaty)[1454]. These were granted FDA emergency use authorization (EUA) in December 2020, in addition to the COVID-19 vaccines developed by Janssen and Novavax, which were also authorized in the U.S. for emergency use. The Pfizer/BioNTech (Comirnaty) vaccine received FDA approval[1455] in August 2021. The NIH intramural program also played a central role in the early testing and development of the AstraZeneca COVAX vaccine, developed in a partnership with Oxford University.

To bring these vaccines through development to clinical testing to public uptake, NIH conducted and supported many research projects to test the safety and efficacy of the vaccine candidates.

To test the efficacy of the candidate vaccine mRNA-1273 (the original name of Spikevax), NIAID researchers conducted immunological studies in mice[1456] and rhesus macaques[1457] by exposing them to SARS-CoV-2. The researchers found that two doses of mRNA-1273 prevented COVID-19 and induced robust immune responses in both species, specifically inducing neutralizing antibodies in mice[1458] and rapidly controlling the virus in the upper and lower airways of the macaques.[1459] Additional experiments found that mice that were given two injections of the candidate vaccine and later challenged with SARS-CoV-2 were, after the second injection, protected from viral replication in the lungs and nose. Importantly, mice challenged seven weeks after only a single dose were also protected against viral replication in the lung. These animal studies complemented interim results reported from an NIAID-sponsored phase 1 clinical trial of mRNA-1273 and supported its advance into phase 3 trials. When the phase 3 clinical trial results were released in FY 2021, they confirmed that the vaccine was safe and 94 percent effective at preventing symptomatic COVID-19 in human patients.[1460,1461]

[1453] https://www.nih.gov/news-events/news-releases/statement-nih-barda-fda-emergency-use-authorization-moderna-covid-19-vaccine

[1454] https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19

[1455] https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine

[1456] https://www.niaid.nih.gov/news-events/nih-moderna-investigational-covid-19-vaccine-shows-promise-mouse-studies

[1457] https://www.niaid.nih.gov/news-events/experimental-covid-19-vaccine-protects-upper-and-lower-airways-nonhuman-primates

[1458] Corbett KS, et al. *Nature.* 2020 Oct;586(7830):567-571. PMID: 32756549.

[1459] Corbett KS, et al. *N Engl J Med.* 2020 Oct 15;383(16):1544-1555. PMID: 32722908.

[1460] https://www.niaid.nih.gov/news-events/peer-reviewed-report-moderna-covid-19-vaccine-publishes

[1461] Baden LR, et al. *N Engl J Med.* 2021 Feb 4;384(5):403-416. PMID: 33378609.

In addition to candidate vaccine design, NIH also developed adjuvants, substances that are formulated as part of a vaccine, to boost immune responses and enhance a vaccine's effectiveness. One such adjuvant developed with funding from NIH contributed to the success of the highly efficacious COVAXIN COVID-19 vaccine, which roughly 25 million people have received to date in India and elsewhere.[1462]

Once public uptake of vaccines was underway, researchers pivoted quickly to start evaluating the effectiveness of vaccines in real-world conditions, such as in nursing facilities where COVID-19 cases surged.

An NIA-supported study found that mRNA COVID-19 vaccines decreased the number of new COVID-19 cases in both vaccinated and unvaccinated nursing home residents.[1463] Using HER data from 280 nursing homes across 21 states, researchers analyzed new cases of SARS-CoV-2 infection in February and March 2021 among more than 18,000 vaccinated and nearly 4,000 unvaccinated residents. Among vaccinated individuals, the number of new cases decreased from 4.5 percent to 1.4 percent two weeks after the first dose, with a subsequent decrease from 1.0 percent to 0.3 percent two weeks after the second dose. Unvaccinated individuals also showed significant reductions in the number of new cases. These findings suggested that widespread vaccination in nursing facilities can decrease new infections among vulnerable older adults, even among those unable to get vaccinated themselves.

In summer 2020, it became clear that vaccine hesitancy would be an issue in implementing a massive vaccine roll-out once any vaccines were granted an EUA by the FDA. To respond to this challenge, a NIH-wide planning workgroup led by NCI and OBSSR convened an expert panel of leaders in the social and behavioral sciences and in public health to summarize evidence-informed communication strategies in support of national coronavirus vaccine distribution efforts across federal agencies and their state and local partners.[1464] In December 2020, NIH released its report entitled, *COVID-19 Vaccination Communication: Applying Behavioral and Social Science to Address Vaccine Hesitancy and Foster Vaccine Confidence*.[1465] As its basis, the report reinforces key foundational principles of health communications, such as coordinated and consistent messaging, building trust through partnerships, tailoring messaging to different levels of health literacy, and prioritizing equity in all communications efforts. The report also provides guidance for vaccine communications with specific groups, including health care professionals, essential workers outside the healthcare system, older adults, individuals living in congregate care settings, and communities of color. Guidance on how to respond effectively to vaccine miscommunication based on prior research also is addressed.

[1462] https://www.nih.gov/news-events/news-releases/adjuvant-developed-nih-funding-enhances-efficacy-indias-covid-19-vaccine

[1463] White EM, et al. *N Engl J Med.* 2021 Jul 29;385(5):474-476. PMID: 34010526.

[1464] https://obssr.od.nih.gov/news-and-events/news/director-voice/nih-releases-report-summarizing-research-vaccine-communication

[1465] *COVID-19 Vaccination Communication: Applying Behavioral and Social Science to Address Vaccine Hesitancy and Foster Vaccine Confidence.* https://obssr.od.nih.gov/sites/obssr/files/inline-files/OBSSR_VaccineWhitePaper_FINAL_508.pdf

Population Effects

From the start of the COVID-19 pandemic, it became apparent that there were consistent differences in COVID-19 prevalence and mortality across different age, racial, and ethnic groups, and among specific populations (e.g., people with asthma or diabetes). NIH and its partners worked to urgently address the impacts of COVID-19 on populations that are underserved and experiencing health disparities.

Health Disparities

From FY 2019–2021, NIH researchers worked to identify populations at high-risk for COVID-19 to better understand the causes of these health disparities as they emerged during the COVID-19 pandemic.

Inequalities in SARS-CoV-2 infection, COVID-19 hospitalization, and death, in under-studied, under-represented, and under-reported groups of people are severe. A growing number of studies have assessed the impact of individual risk factors, but few studies have assessed which factors are the greatest drivers of COVID-19 disparities from a wider perspective. In FY 2021, NIEHS announced the Women's Health Awareness Community Resiliency, Environmental Action, and Collaborations for Health Equity study to understand the long-term impacts of COVID-19 on minority women and their families, to assist in developing community-based programs to help in recovery.[1466]

The COVID-19 pandemic intersected with the ongoing opioid overdose epidemic, each with the potential to exacerbate the effects of the other. In FY 2020, NIDA released a NOSI to alert researchers with existing grants of NIDA's interest in supporting applications for administrative supplements and urgent competitive revisions that could be used to investigate those aspects of COVID-19 that intersect with substance use, and in related areas of NIDA's research portfolio, such as HIV.[1467] NIDA supported more than 100 studies at the intersection of COVID-19 and substance use, with projects ranging from assessing the virus' impact on individuals with substance use disorder, including those who are homeless or incarcerated, to basic research to investigate potential interactions between drugs and SARS-CoV-2, including effects on the immune system.[1468]

Between December 2020 and August 2021—the period when COVID-19 vaccines were first offered to the public—a NIDA-funded study found that co-occurring health conditions and adverse socioeconomic determinants of health, which are more common in people with substance use disorders, appeared to be largely responsible for the increased risk of SARS-CoV-2 breakthrough infections.[1469] An analysis of EHRs of nearly 580,000 fully vaccinated people in the U.S. found that the risk of SARS-CoV-2 breakthrough infection among vaccinated patients with substance use disorders was higher than the risk among

[1466] NCT04983251. https://clinicaltrials.gov/ct2/show/NCT04983251
[1467] NOT-DA-20-047. https://grants.nih.gov/grants/guide/notice-files/NOT-DA-20-047.html
[1468] https://archives.nida.nih.gov/news-events/noras-blog/2020/06/nida-researchers-adapt-their-projects-to-study-covid-19
[1469] https://nida.nih.gov/news-events/news-releases/2021/10/people-with-substance-use-disorders-may-be-at-higher-risk-for-sars-cov-2-breakthrough-infections

vaccinated people without substance use disorders.[1470] These results are important because people with substance use disorder may be particularly vulnerable to COVID-19 and related severe outcomes.

Maternal Health and Pregnancy

Metabolic changes in pregnancy can affect how an individual responds to infection or vaccination. NICHD's historical focus on vulnerable populations enabled established research infrastructure to rapidly pivot and address the impact of COVID-19 in children, pregnant women, individuals with disabilities, and underserved communities.

In FY 2020, NICHD launched a study through the Global Network for Women's and Children's Health Research to track the prevalence and impact of SARS-CoV-2 infection among approximately 16,000 pregnant participants in seven low- and middle-income countries.[1471] The study will follow participants through pregnancy and in the 12 months after childbirth to compare maternal, fetal, and newborn outcomes of participants who have been infected with the virus to those of pregnant participants who have not been infected.

In FY 2021, NICHD's Maternal Fetal Medicine Units Network evaluated more than 1,200 pregnant patients with COVID-19 who delivered at 33 U.S. hospitals between March 1 and July 30, 2020. The researchers, as part of the Gestational Research Assessments for COVID-19 study, demonstrated that pregnant patients who experienced severe symptoms of COVID-19 had a higher risk of complications during and after pregnancy.[1472] Compared with COVID-19 patients without symptoms, those with severe symptoms were at higher risk for cesarean delivery, postpartum hemorrhage, hypertensive disorders of pregnancy, and preterm birth.

Many ICs across NIH conducted or supported studies to understand how pregnancy and breastfeeding affected immune responses to COVID-19 vaccines.

A study supported by NICHD, NHLBI, and NIAID showed that current vaccines (Spikevax and Comirnaty) to prevent COVID-19 are highly effective in producing antibodies in pregnant people, resulting in more antibodies than what is generated from a natural SARS-CoV-2 infection.[1473,1474] Moreover, antibodies produced after vaccination were present in breastmilk and travel across the placenta, indicating that vaccination during pregnancy will also confer immunity to newborns. It is important to note that the vaccines were made available to pregnant people after the vaccines received approval; no vaccine was tested on a pregnant patient, due to safety concerns. These findings indicate that the vaccines promote strong immunity to SARS-CoV-2, similar to that seen in non-pregnant individuals. Another study funded by NCATS, NICHD, and NIAID that surveyed more than 17,000 pregnant and lactating individuals who

[1470] Wang L, et al. *World Psychiatry.* 2022 Feb;21(1):124-132. PMID: 34612005.
[1471] https://www.nichd.nih.gov/newsroom/news/090120-COVID19-pregnancy
[1472] https://www.nichd.nih.gov/newsroom/news/012821-GRAVID
[1473] https://www.nichd.nih.gov/newsroom/news/032921-COVID-vaccine-pregnancy
[1474] Gray KJ, et al. *Am J Obstet Gynecol.* 2021 Sep;225(3):303.e1-303.e17. PMID: 33775692.

received the COVID-19 vaccine showed that the individuals did not experience symptoms any more severe than their non-pregnant counterparts.[1475]

Age-Specific Factors

Shortly after the beginning of the COVID-19 pandemic, anecdotal reports of age-specific effects and symptoms began to emerge suggesting that children were not affected by the virus or that only the elderly need be concerned about severe COVID-19 disease or death. NIH quickly utilized its resources to support research and address these apparently age-specific questions of SARS-CoV-2 infection and COVID-19.

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare condition that usually affects school-age children who were infected with SARS-CoV-2 and who experienced only mild COVID-19 symptoms or no symptoms at all. MIS-C is marked by severe inflammation of two or more parts of the body, including the heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal organs. Its symptoms overlap with Kawasaki disease, and treatments for MIS-C are guided in part by what is known about treating Kawasaki disease. Since May 2020, there have been more than 7,800 total MIS-C patients meeting the case definition, with 66 deaths from MIS-C. The CARING for Children with COVID initiative[1476] aims to identify risk factors for MIS-C, aligning multiple cohort studies on pharmacokinetics of understudied drugs, long-term outcomes, and immunologic pathways. It is supported by NICHD, NHLBI, and NIAID, respectively, to leverage the power of their clinical networks.

Evaluating strategies designed to curb the spread of SARS-CoV-2 in schools and businesses has been a priority of NIH and its partners.

In FY 2021, a report issued by the ABC Science Collaborative, which is coordinated by a CTSA program funded in part by NCATS and NICHD, showed that North Carolina schools were highly successful in preventing the transmission of COVID-19 within school buildings. This finding offers science-based learnings that can help the Nation's schools limit SARS-CoV-2 spread.[1477] The report found that the schools that had in-person learning paired with masking and minimal physical distancing succeeded in limiting SARS-CoV-2 spread, with proper masking being the most effective mitigation strategy in the absence of sufficient vaccination levels.

Relative to younger age groups, older adults are more susceptible to adverse outcomes from COVID-19, and both age and other risk factors may heighten their overall susceptibility.

NIH-funded research from multiple ICs suggests that COVID-19 may present atypically among older adults, meaning with symptoms other than those typically associated with COVID-19 (fever, cough, and shortness of breath). This is a major concern because it could result in less aggressive treatment, which could shape survival and recovery outcomes among older patients. In FY 2021, researchers showed that 28 percent of older adults with COVID-19 presented to an emergency department with delirium and that 37 percent of

[1475] Kachikis A, et al. *JAMA Netw Open*. 2021 Aug 2;4(8):e2121310. PMID: 34402893.
[1476] https://caring4kidswithcovid.nih.gov/
[1477] https://abcsciencecollaborative.org/the-abcs-of-north-carolinas-plan-a/

these delirious patients did not show typical COVID-19 symptoms, such as fever or cough.[1478] Delirium in this context was also associated with an increased risk of death.

In addition, NIA-supported studies further demonstrated that advancing age predicts heightened risk of death among critically ill COVID-19 patients. In a multicenter cohort study of more than 2,200 patients in 65 U.S. hospitals from March to April 2020, investigators saw that patients 60–69 years of age had three times greater odds of death than those under age 40, patients 70–79 had five times greater odds of death, and patients 80 years of age and older had 11 times greater odds of death.[1479] Male sex, higher body mass index, coronary artery disease, active cancer, and hypoxemia (low blood oxygen) were also associated with an increased risk of death in this study. Another NIA-supported analysis of 5,700 hospitalized COVID-19 patients likewise showed progressively higher mortality rates with advancing age, in addition to identifying higher rates of mortality in men versus women across age groups.[1480] The trend of increased COVID-19-related mortality with advancing age has also been observed within nursing home populations.[1481]

NIA-supported research has shown that people with dementia have a higher risk of developing COVID-19, are more likely to require hospitalization following a COVID-19 diagnosis, and are more likely to have severe or fatal cases of COVID-19 compared with those without dementia.[1482] Specifically, those living with dementia were twice as likely to develop COVID-19 relative to people without dementia, and this risk was nearly three times higher among Black patients with dementia than among White patients with dementia. In the six months following a COVID-19 diagnosis, 25 percent of patients without dementia were hospitalized. That factor rose to 54 percent in White patients with dementia, and to 73 percent in Black patients with dementia. Patients of either race with dementia were almost four times more likely to die from COVID-19 than patients without dementia. Similarly, the severity of cognitive impairment among nursing home residents has been shown to correlate with SARS-CoV-2 fatality rates, with more severe impairment predicting greater odds of death.[1483]

Other Emerging Infectious Diseases

In addition to supporting research on influenza, EVD, Zika, and antimicrobial resistance, NIH also funds research on other emerging infectious diseases and infectious agents, such as prions, parasites, mammal-borne viruses, and those with unknown etiology.

Prions

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of rare, fatal brain diseases that affect animals and humans. They are caused by an infectious agent known as a prion

[1478] Kennedy M, et al. *JAMA Netw Open.* 2020 Nov 2;3(11):e2029540. PMID: 33211114.
[1479] Gupta S, et al. *JAMA Intern Med*. 2020 Nov 1;180(11):1436-1447. Erratum in: *JAMA Intern Med*. 2020 Nov 1;180(11):1555. Erratum in: *JAMA Intern Med.* 2021 Aug 1;181(8):1144. PMID: 32667668.
[1480] Richardson S, et al. *JAMA*. 2020 May 26;323(20):2052-2059. Erratum in*: JAMA*. 2020 May 26;323(20):2098. PMID: 32320003.
[1481] Panagiotou OA, et al. *JAMA Intern Med*. 2021 Apr 1;181(4):439-448. PMID: 33394006.
[1482] Wang Q, et al. *Alzheimers Dement.* 2021 Aug;17(8):1297-1306. PMID: 33559975.
[1483] Panagiotou OA, et al. *JAMA Intern Med*. 2021 Apr 1;181(4):439-448. PMID: 33394006.

protein, which is derived from a misfolded version of a normal host protein. Prion diseases include bovine spongiform encephalopathy (BSE or "mad cow" disease) in cattle, Creutzfeldt-Jakob disease (CJD) and variant CJD in humans, scrapie in sheep, and chronic wasting disease (CWD) in deer, elk, moose, and reindeer.[1484] Currently, there are no FDA-licensed preventive or therapeutic treatments for prion diseases.

CJD affects about 1 in 1 million people each year. It can arise spontaneously, result from a hereditary mutation within the prion gene, or arise due to infection, for example, from eating contaminated meat products.[1485] In FY 2021, NIAID researchers further developed a human cerebral organoid system to study and screen drugs for potential CJD treatment.[1486,1487]

Scrapie is a fatal, degenerative disease affecting the central nervous system of animals. Scientists using an experimental treatment have slowed the progression of scrapie in laboratory mice and greatly extended the rodents' lives.[1488] The scientists used antisense oligonucleotides (ASOs), which are synthetic compounds that inhibit the formation of specific proteins.[1489] The researchers injected ASOs into the spinal fluid of mice already infected with scrapie or that were to be challenged with scrapie proteins within weeks of the injection. Mice injected with ASOs did not show signs of disease and lived longer than mice who were not treated with ASOs. Researchers plan to expand their studies to human prion diseases.

About a decade ago, NIH scientists developed an ultrasensitive test (RT-QuIC) to detect CJD and other prion diseases.[1490] Since then, they have repeatedly improved and adapted it to detect abnormal clusters of tau protein, which contributes substantially to the disease processes of Alzheimer's disease and chronic traumatic encephalopathy, a condition found in athletes, military veterans, and others with a history of repetitive brain trauma.[1491] This advance could lead to early diagnosis of prion and other neurodegenerative conditions and open new research into how these diseases originate.

Parasites

Human African Trypanosomiasis (HAT, or Sleeping Sickness) is endemic to sub-Saharan Africa, affecting mostly poor populations, with 8.5 million people estimated to be at risk across 36 countries.[1492] WHO has a goal of eradication of disease, and acoziborole represents a cost-effective, easy-to-administer oral therapy that could vastly improve accessibility and compliance compared to existing therapies. The NCATS Therapeutics for Rare and Neglected Diseases program completed the critical toxicology studies necessary to enable the partners at the Drugs for Neglected Diseases initiative to complete pivotal phase 2/3

[1484] https://www.cdc.gov/prions/index.html
[1485] https://www.ninds.nih.gov/creutzfeldt-jakob-disease-fact-sheet
[1486] https://www.niaid.nih.gov/news-events/nih-scientists-use-human-cerebral-organoid-test-drug-deadly-brain-disease
[1487] Groveman BR, et al. *Sci Rep.* 2021 Mar 9;11(1):5165. PMID: 33727594.
[1488] https://www.niaid.nih.gov/news-events/experimental-treatment-slows-prion-disease-extends-life-mice
[1489] Raymond GJ, et al. *JCI Insight.* 2019 Jul 30;5(16):e131175. PMID: 31361599.
[1490] https://www.niaid.nih.gov/news-events/nih-developed-test-detects-protein-associated-alzheimers-and-cte
[1491] Kraus A, et al. *Acta Neuropathol.* 2019 Apr;137(4):585-598. PMID: 30570675.
[1492] https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)

trials.[1493] Acoziborole is now moving toward formal registration, and Sanofi and WHO will provide the drug for free to patients through the public health systems of the affected countries.

Mammal-Borne Viruses

Many viruses are zoonotic, meaning that they are spread between animals and people. For example, fruit bats are the natural host for Nipah virus, and while most cases of Nipah are transmitted via animals, person-to-person transmission can occur. People contract Lassa virus through contact with infected *Mastomys* rats and through exposure to an infected person's bodily fluids.[1494] Currently, there are no FDA-licensed vaccines or treatments for either Nipah virus or Lassa virus infections.

In FY 2019, the experimental antiviral drug remdesivir completely protected four African green monkeys from a lethal dose of Nipah virus.[1495] NIAID conducted the monkey studies with laboratory serology and pathology support from CDC. Animals infected with a lethal dose of Nipah virus received a first dose of intravenous remdesivir 24 hours after infection and then a daily intravenous dose for a total of 12 consecutive days.[1496] Next, scientists plan to evaluate delayed drug administration to determine how long after infection the animals can be treated successfully. Remdesivir is the second experimental treatment, after monoclonal antibody m102.4, which has been shown to prevent severe Nipah virus disease in a monkey model when administered after the animals are infected.

While there are currently no FDA-approved vaccines for Lassa fever or Nipah virus disease, NIH scientists have worked during FY 2019–2021 to design and test several candidates that could change that.

Another mammal-borne virus, rabies virus, is a significant health burden in regions where Nipah virus and Lassa virus are endemic. In FY 2019, inactivated rabies virus was used as a vector, or carrier, for two different candidate vaccines for Nipah virus and Lassa virus; the candidate vaccines then express surface proteins from both viruses that prompt an immune response to both viruses.[1497] Mice inoculated with the candidate vaccine against both Nipah and rabies viruses developed neutralizing antibodies against Nipah virus, indicating that this experimental vaccine may be used in the future to protect humans against both Nipah and rabies viruses.[1498] The candidate vaccine used against both Lassa and rabies viruses elicited antibodies against both viruses in mouse and guinea pig models and protected guinea pigs from Lassa virus after being exposed to the virus 58 days after vaccination.[1499] Combination vaccines like these offer significant advancements in protecting people from infectious diseases in resource-limited regions.

[1493] https://ncats.nih.gov/trnd/projects/active/acoziborole-human-african-trypanosomiasis
[1494] https://www.cdc.gov/vhf/lassa/transmission/index.html
[1495] https://www.niaid.nih.gov/news-events/media-availability-experimental-drug-completely-effective-against-nipah-virus-infection
[1496] Lo MK, et al. *Sci Transl Med*. 2019 May 29;11(494):eaau9242. PMID: 31142680.
[1497] https://www.nih.gov/news-events/news-releases/scientists-develop-novel-vaccine-lassa-fever-rabies
[1498] Keshwara R, et al. *NPJ Vaccines*. 2019 Apr 15;4:15. Erratum in: *NPJ Vaccines*. 2019 May 13;4:18. PMID: 31016033.
[1499] Abreu-Mota T, et al. *Nat Commun.* 2018 Oct 11;9(1):4223. PMID: 30310067.

In FY 2020, NIAID-supported investigators generated two different Lassa fever vaccine candidates.[1500, 1501] Both vaccine candidates are live-attenuated, meaning that they have been altered to generate a protective immune response without causing disease, and both successfully protected animals from disease when the animals were inoculated prior to being exposed to a lethal dose of Lassa virus. These results support future testing of both vaccine candidates in nonhuman primate models of Lassa fever.

In recent years, there have been surges in the number of cases of Lassa fever in Nigeria, causing experts to have concerns that there could be a particularly infectious strain of the virus or human-to-human transmission of the disease occurring. This concern led a team of researchers, including members of the NIH Common Fund-supported Human Heredity and Health in Africa (H3Africa) program, to conduct a genetic analysis of viruses in samples collected from patients infected with the Lassa virus.[1502] Lassa virus genomes of patients from the 2017–2018 outbreak and the 2015–2017 seasons were analyzed to better understand these surges.[1503] Researchers discovered that Lassa virus genomes from 2018 were drawn from a diverse range of viruses previously observed in Nigeria, rather than from a single dominant strain, indicating that a single virus strain was not driving the outbreak.[1504] Further epidemiological analyses of the samples from 2018 showed limited support for human-to-human transmission but had features consistent with many independent zoonotic transmissions. The research serves as a model for investigating infectious disease emergencies by combining genomic information with traditional epidemiological data to inform response strategies.

Unknown Etiology

When new infectious diseases emerge with unknown origins or causes, NIH scientists start at the beginning to establish a foundation of understanding of the disease, to provide answers to patients and their families.

Enteroviruses are a group of viruses that cause a number of infectious illnesses that are common and usually mild.[1505] Despite an epidemiological link between enterovirus circulation and cases of acute flaccid myelitis (AFM), an uncommon but serious neurologic condition that affects the nervous system and causes the muscles and reflexes in the body to become weak,[1506] evidence of direct causality has not been found. A new study analyzing samples from patients with and without AFM provides additional evidence for an association between the rare but often serious condition that causes muscle weakness and paralysis, and infection with non-polio enteroviruses.[1507] Enterovirus-specific antibodies were detected in the CSF of 79 percent (11 of 14) of the AFM cases. Of those, six samples were positive for enterovirus-D68, strongly indicating that enterovirus had been in the central nervous system, even though it had not been detected

[1500] Cai Y, et al. *mBio.* 2020 Feb 25;11(1):e00039-20. PMID: 32098811.
[1501] Cai Y, et al. *mBio.* 2020 Mar 24;11(2):e00186-20. PMID: 32209677.
[1502] https://commonfund.nih.gov/globalhealth/programhighlights#lassa
[1503] https://www.nih.gov/news-events/news-releases/genomic-analysis-offers-insight-into-2018-nigeria-lassa-fever-outbreak
[1504] Siddle KJ, et al. *N Engl J Med*. 2018 Nov 1;379(18):1745-1753. PMID: 30332564.
[1505] https://www.cdc.gov/dotw/enteroviruses/index.html
[1506] https://www.cdc.gov/acute-flaccid-myelitis/about-afm.html#:~:text=Acute%20flaccid%20myelitis%20(AFM)%20is,and%202018%20in%20the%20U.S.
[1507] https://www.niaid.nih.gov/news-events/enterovirus-antibodies-detected-acute-flaccid-myelitis-patients

by VirCapSeq-VERT, which can detect any viral genetic material that is at least 60 percent similar to any known vertebrate virus.[1508] While other etiologies of AFM continue to be investigated, this study provides further evidence that enterovirus infection may be a factor in AFM. In the absence of direct detection of a pathogen, antibody evidence of pathogen exposure within the central nervous system can be an important indicator of the underlying cause of disease.

Infectious Disease and Biodefense Infrastructure

Organized infrastructure is essential to coordinating the research required to understand the biology of infectious diseases and develop and test interventions that can curb disease outbreaks and protect public health. The examples below complement the research advances previously mentioned in this section, and are examples of NIH-funded activities that enable research through coordination, infrastructure, and capacity building.

HIV/AIDS

During FY 2019–2021, NIH held several workshops to bring together the many ICs and OD offices that fund HIV/AIDS research. One workshop focused on HIV-associated comorbidities, co-infections, and complications (CCCs), with a further focus on fostering discussion among experts from different fields and disciplines and exploring interrelationships among multiple HIV-associated CCCs.[1509] A second workshop was focused on strengthening the impact of community health workers on HIV care and viral suppression in the U.S.[1510] This work led to the launch of a NINR initiative with NIMH and NIDA to establish evidence for engaging community health workers in the HIV treatment cascade, with a goal of improving access, treatment literacy, and adherence support, and retention in HIV care, ultimately closing the gap between ART prescription and viral suppression. A third workshop on HIV-related intersectional stigma research advances and opportunities aimed to advance HIV prevention and treatment science, inform the EHE in the U.S. initiative,[1511] and bolster HIV prevention and treatment efforts worldwide.[1512]

Every year, NIH, led by OAR, recognizes World AIDS Day, gathering the scientific, health care, and patient communities together to recognize the milestones achieved through science and to pay tribute to the more than 32 million people who have died from AIDS-related illness globally (including 700,000 Americans) and to support EHE in the U.S. and worldwide. In 2019, the theme was Community and NIH: In Partnership to End the HIV Epidemic, and the event featured speakers from communities touched by HIV/AIDS, who discussed how they and the NIH can work together to eradicate the disease.[1513,1514] In 2020, the theme was Science and Community: Working Together to Prepare for the Unexpected, and the

[1508] Mishra N, et al. *mBio*. 2019 Aug 13;10(4):e01903-19. PMID: 31409689.
[1509] https://www.nhlbi.nih.gov/events/2019/hiv-associated-comorbidites-co-infections-complications-workshop
[1510] https://oar.nih.gov/about/directors-corner/nih-conference-strengthening-impact-community-health-workers-hiv-care-and-viral
[1511] *NIH HIV/AIDS Executive Committee FY 2019 EHE in the U.S. Report.* https://www.oar.nih.gov/sites/default/files/OAR-NAEC-EHE-WG-508.pdf
[1512] Workshop Summary. https://www.nimh.nih.gov/sites/default/files/documents/nih_oar_and_nimh_hiv-related_intersectional_stigma_final_workshop_summary_final_508.pdf
[1513] https://www.oar.nih.gov/news-and-events/world-aids-day-2019
[1514] https://www.nih.gov/news-events/news-releases/nih-statement-world-aids-day-2019

event featured speakers who reflected on lessons learned from HIV that have prepared the Nation to address other unexpected public health events, and who emphasized the importance of building the capacity of current and future generations of HIV researchers and advocates.[1515,1516] In 2021, NIH recognized the 40th anniversary of the landmark *CDC Morbidity and Mortality Weekly Report*, which first recognized the syndrome of diseases later named AIDS.[1517,1518] Over these past 40 years, much of the progress that guides the response to the HIV/AIDS pandemic has emerged from research funded by the NIH—and that has helped turn a once-fatal disease into the manageable chronic illness that it is today.

In FY 2020, NIAID announced that clinical investigators and institutions will lead four NIH HIV clinical trials networks over the next seven years.[1519] NIAID also awarded grants to 35 U.S. and international institutions selected as HIV clinical trials units. NIAID and co-funding NIH ICs intend to provide approximately $375.3 million in the first year to support the networks.

In FY 2021, NIH released a funding opportunity to stimulate research on interventions to reduce HIV/AIDS-associated stigma and its impact on the prevention and treatment of HIV/AIDS and on the quality of life of people with HIV/AIDS.[1520] The overall goals are to better understand how to reduce stigma as a factor in HIV transmission, eliminate or mitigate the aspects of stigma that limit beneficial health outcomes for the infected and at-risk individuals and communities, and initiate exploratory studies to determine the feasibility of stigma interventions related to HIV prevention, treatment and/or care in low- and middle-income countries.

In FY 2021, NIH renewed grants to the seven regional centers that comprise the International epidemiology Databases to Evaluate AIDS (IeDEA) program, awarding $20.8 million in first-year funding.[1521] The 15-year-old IeDEA program efficiently advances knowledge about HIV by pooling and analyzing de-identified health data from more than two million people on five continents with HIV, to answer research questions that individual studies cannot address. The grants are expected to last five years and total an estimated $100 million.

Influenza

Because influenza has pandemic potential, collaborative research networks are essential for influenza research and surveillance.

In FY 2019, NIH established the Collaborative Influenza Vaccine Innovation Centers (CIVICs) program, a new network of research centers that will collaborate in a coordinated, multidisciplinary effort to develop more durable, broadly protective, and longer-lasting influenza vaccines.[1522] The CIVICs network will develop so-called universal influenza vaccines, which could provide longer-lasting protection than current

[1515] https://oar.nih.gov/news-and-events/meetings-events/world-aids-day-2020
[1516] https://www.oar.nih.gov/nih-statement-on-world-aids-day-2020
[1517] https://www.oar.nih.gov/reflect-recommit-reenergize-reengage-four-forty
[1518] https://www.oar.nih.gov/news-and-events/meetings-events/world-aids-day-2021
[1519] https://www.niaid.nih.gov/news-events/nih-announces-restructured-hiv-clinical-trials-networks
[1520] Research Project Grant, PAR-21-344. https://grants.nih.gov/grants/guide/pa-files/PAR-21-344.html
[1521] https://www.niaid.nih.gov/news-events/nih-awards-more-20-million-international-hiv-database-centers
[1522] https://www.niaid.nih.gov/news-events/nih-forms-new-collaborative-influenza-vaccine-research-network

vaccines and against a wider variety of influenza viruses. The CIVICs network also will explore approaches to improve seasonal influenza vaccines, such as by testing alternative vaccine platforms or incorporating new adjuvants (substances added to vaccines to boost immunity).

In FY 2021, NIAID established a network of research sites to study the natural history, transmission, and pathogenesis of influenza, and to provide an international research infrastructure to address influenza outbreaks. The program, called the Centers of Excellence for Influenza Research and Response (CEIRR), is expected to be supported for seven years by NIAID contracts to five institutions. Funding for the first year of the contracts will total approximately $24 million. CEIRR will replace the Centers of Excellence for Influenza Research and Surveillance program, which was supported by contracts that concluded on March 31, 2021.

Emerging Infectious Diseases

Infectious diseases know no geographic boundaries, and global health requires coordination and collaboration that is both global and transparent.

In FY 2020, NIAID awarded 11 grants with a total first-year value of approximately $17 million to establish the Centers for Research in Emerging Infectious Diseases.[1523] The global network will involve multidisciplinary investigations that focus on how and where viruses and other pathogens emerge from wildlife and spillover to cause disease in people. NIAID intends to provide approximately $82 million over five years to support the network.

Antibiotic Resistance

As antibiotic-resistant bacteria become more urgent threats worldwide, NIAID is funding over seven years for the Antibacterial Resistance Leadership Group.[1524] This global consortium of scientific experts leads a comprehensive clinical research network overseeing research on important scientific questions related to antibacterial resistance.

During FY 2019–2021, NLM's National Center for Biotechnology Information (NCBI) Pathogen Detection project[1525] was used to analyze multiple outbreaks stemming from pathogens such as *Salmonella*, *Clostridioides difficile*, and *Listeria*, among others.[1526] The project integrates bacterial and fungal pathogen genomic sequences[1527] from numerous ongoing surveillance and research efforts, whose sources include food, environment (such as water or production facilities), and patient samples. The project provides open-access, easy-to-use web results of the relatedness of pathogen isolates to aid in disease outbreak investigations. In addition, in support of the Combating Antibiotic Resistant Bacteria (CARB) initiative, the Pathogen Detection project provides a system to detect the genes responsible for antimicrobial resistance in the submitted sequences, the results of which are used by the National Antibiotic Resistance Monitoring

[1523] https://www.niaid.nih.gov/news-events/niaid-establishes-centers-research-emerging-infectious-diseases
[1524] https://www.nih.gov/news-events/news-releases/nih-renews-funding-antibacterial-resistance-leadership-group
[1525] https://www.ncbi.nlm.nih.gov/pathogens/
[1526] https://www.ncbi.nlm.nih.gov/pathogens/success_stories/
[1527] https://www.ncbi.nlm.nih.gov/pathogens/organisms/

System and have been used by scientists researching antimicrobial resistance. To date, more than one million isolates have been sequenced and analyzed in the system.

COVID-19

From FY 2019–2021, the COVID-19 pandemic required NIH to move rapidly to support research by standing up new and leveraging existing infrastructure within the biomedical enterprise. NIH issued funding notices, created collaboration centers and hubs, developed resources for data sharing and community engagement, and invested in capacity-building programs—all with the focus on building the foundation required to understand SARS-CoV-2 and its effects on specific populations, such as those experiencing health disparities and those considered essential workers, and to develop diagnostics, treatments, and vaccines. Highlighting the convergence between the HIV and COVID-19 pandemics and the research challenges they both pose, OAR established the Taskforce on COVID-19 and HIV.[1528] The purpose of this taskforce is to provide recommendations on programmatic, scientific, and operational focus areas and action plans that are relevant to HIV and COVID-19 research.

Building Capacity

The RADx initiative aims to speed innovation in the development, commercialization, and implementation of technologies for COVID-19 testing.[1529] RADx has four programs focused on different facets of diagnostics: RADx Tech will speed the development, validation, and commercialization of innovative point-of-care and home-based tests, as well as improve clinical laboratory tests, that can directly detect the virus; RADx-UP will seek to understand the factors associated with disparities in COVID-19 morbidity and mortality and to lay the foundation to reduce disparities for those underserved and vulnerable populations who are disproportionately affected by, have the highest infection rates of, and/or are most at risk for complications or poor outcomes from the COVID-19 pandemic; RADx Radical (RADx-rad) will support new, non-traditional approaches, including rapid detection devices and home-based testing technologies that address current gaps in COVID-19 testing; and RADx Advanced Technology Platforms (RADx-ATP) seeks to increase testing capacity and throughput by identifying existing and late-stage testing platforms for COVID-19 that are advanced enough to achieve rapid scale-up or expanded geographical placement in a short amount of time.[1530]

Together, RADx Tech and RADx-ATP have resulted in 44 technologies that have been granted EUAs by FDA, culminating in over 1.9 billion COVID-19 test products.[1531] Relatedly, the RADx Independent Test Assessment Program (ITAP) was developed to accelerate FDA evaluation of over-the-counter COVID-19 tests with potential for large-scale manufacturing.[1532] The goal is to accelerate the availability of high-quality, accurate, and reliable over-the-counter tests to the public as quickly as possible. ITAP has

[1528] Office of AIDS Research Advisory Council Fifty-Fourth Meeting Report. https://www.oar.nih.gov/sites/default/files/OARAC_54th_Meeting_Minutes_508.pdf#page=7
[1529] https://www.nih.gov/news-events/news-releases/nih-mobilizes-national-innovation-initiative-covid-19-diagnostics
[1530] https://www.nih.gov/research-training/medical-research-initiatives/radx
[1531] https://www.nibib.nih.gov/covid-19/radx-tech-program
[1532] https://www.nibib.nih.gov/covid-19/radx-tech-program/ITAP

produced five technologies that were granted EUAs by FDA, and more than one million tests have been made available to the public.

NIH has also invested in building capacity to aid state and local governments in their decision making throughout the pandemic. NIH scientists created the COVID-19 Pandemic Vulnerability Index (PVI), which is an online data visualization dashboard that calculates risk profiles, called PVI scorecards, for every county in the U.S.[1533] The dashboard offers an effective means of communicating data to scientists, policymakers, and the public. Additionally, in FY 2021, FIC, in collaboration with multiple U.S. and international academic institutions and government agencies, created the COVID-19 Scenario Modeling Hub[1534] to generate projections of COVID-19 hospitalizations, cases, and deaths in the U.S., at national and state levels. The hub has delivered 13 rounds of long-term scenario-based projections of COVID-19 for policymakers and the public. Projections are delivered monthly to public health stakeholders.

In addition to research, regulatory, and policy capacity, NIH has been investing in building workforce capacity in response to the COVID-19 pandemic. FIC's Genomic Epidemiology Training Program has taught 237 participants at 52 institutes in 23 countries the techniques of genomic epidemiology for SARS-CoV-2 during the pandemic.[1535] The NIEHS Worker Training Program (WTP) has been addressing preparedness and response efforts since 2001. In FY 2020, the semi-annual WTP Awardee Meeting explored the training and protective measures that worked best during previous infectious disease outbreaks to inform worker protection during the current COVID-19 outbreak.[1536] WTP awardees provided occupational biological safety training to workers during the anthrax attacks (2001), the H5N1 influenza outbreak (2007), and the H1N1 avian influenza outbreak (2009). Awardees also provided mold remediation training following Hurricanes Katrina (2005) and Sandy (2012) and EVD preparedness training (2013-2015). All this knowledge was applied to COVID-19 preparedness efforts.

Leveraging Research Funding to Address the Pandemic

In order to quickly support research on SARS-CoV-2 and the COVID-19 pandemic, NIH used several different mechanisms of research funding and support for NIH researchers.

The NIH Common Fund used $30 million to prevent, prepare for, and respond to COVID-19, domestically or internationally. The NIH Common Fund issued immediate funding opportunities in FY 2020 for active NIH Common Fund researchers to conduct SARS-CoV-2 and COVID-19 research.[1537] Eight awards were issued[1538] through these funding opportunities, resulting in research efforts to build a user-friendly COVID-19 web interface, to investigate causes of inequities in COVID-19 severity, to generate a panel of genetically diverse mice to study COVID-19, to leverage a rapid screen technology to study SARS-CoV-2 immune protection, to screen thousands of well-characterized drugs for their ability to inhibit SARS-CoV-

[1533] Marvel SW, et al. *Environ Health Perspect*. 2021 Jan;129(1):17701. PMID: 33400596.
[1534] https://covid19scenariomodelinghub.org/viz.html
[1535] https://www.fic.nih.gov/Grants/Search/Pages/search-grants.aspx?search=%22genomic%20epidemiology%20research%20training%20program%22
[1536] https://www.niehs.nih.gov/news/events/pastmtg/hazmat/2020/Spring_Meeting/index.cfm
[1537] https://commonfund.nih.gov/covid19
[1538] https://commonfund.nih.gov/TRA/recipients#COVID_Awardees

2 infection, and to develop robotic diagnostic equipment to help reduce the risk of COVID-19 infections in health care workers. The NIH Common Fund also issued five awards in FY 2021 to support exceptionally innovative research on SARS-CoV-2 and COVID-19 through its prestigious Transformative Research Award. Additionally, the NIH ECHO Program Office issued a NOSI to encourage and foster time-sensitive ECHO-wide cohort science projects related to the COVID-19 pandemic.[1539] NIH funded six projects, which include participation from 24 ECHO Pediatric Cohorts or Centers. [1540]

Early in 2020, NIH leadership identified multiple cross-cutting research initiatives in response to the COVID-19 pandemic. One of these cross-cutting initiatives was the formation of the Social, Behavioral, and Economic Health Impacts of COVID-19 (SBE COVID) initiative, which focused on research to improve our understanding of the efficacy and impacts of various mitigation efforts, assess the downstream health and health care access effects from the economic downturn, and evaluate digital and community interventions to ameliorate these health effects.[1541] As part of these efforts, NIH established the NIH SBE COVID Consortium Coordinating Center, which will foster innovation, collaboration, and synergies among researchers funded through the SBE COVID-19 Consortium (U01) program and other relevant NIH-funded studies.

NIH also capitalized on ongoing programs by shifting the focus of the programs to combating COVID-19. The NIH Exploratory/Developmental Research Grant Program supports early-stage conceptual work and feasibility tests in data science, biomedical informatics, and bioinformatics.[1542] In FY 2021, NLM awarded six grants focused on combating COVID-19 by: using road traffic data to identify COVID-19 priority testing locations; analyzing COVID-19 disease course using multi-site large-scale HER data; identifying existing, FDA-approved drugs with clinically protective effects against COVID-19;developing a vaccine informatics system to identify the impact of vaccine debate on immunization rates during the pandemic; assessing COVID-19 susceptibility and severity using X-ray and CT scans; and identifying and understanding drivers of selection bias and information bias in clinical COVID-19 data.

Because the oral cavity presented a route of transmission for SARS-CoV-2, dental practitioners were at high risk of exposure to the virus. NIDCR was able to pivot to address this factor early in the pandemic. Using the already existing National Dental Practice-Based Research Network (PBRN), NIDCR was able to solicit high-priority projects to investigate the transmissibility of SARS-CoV-2 in dental settings, develop methods to prevent transmission, and look at the potential for teledentistry to improve access to care for patients.[1543]

[1539] https://grants.nih.gov/grants/guide/notice-files/not-od-20-107.html
[1540] https://echochildren.org/covid-19/#:~:text=ECHO%20COVID%2D19%20NOSI%20Projects
[1541] https://obssr.od.nih.gov/news-and-events/news/director-voice/nih-behavioral-and-social-science-covid-19-research-funding
[1542] https://www.nlm.nih.gov/ep/GrantExDev.html
[1543] https://www.nidcr.nih.gov/research/covid-19/covid19-studies-PBRN

In FY 2021, NIH awarded nearly $470 million to build a national study population of diverse research volunteers and support large-scale studies on the long-term effects of COVID-19.[1544] NIH launched the Researching COVID to Enhance Recovery (RECOVER) Initiative to learn why some people develop prolonged symptoms (referred to as long-COVID), or develop new or returning symptoms after the acute phase of infection from SARS-CoV-2 (PASC). The most common symptoms include pain, headaches, fatigue, "brain fog," shortness of breath, anxiety, depression, fever, chronic cough, and sleep problems. Data from the RECOVER Initiative will include clinical information, laboratory tests, and analyses of participants in various stages of recovery following SARS-CoV-2 infection. RECOVER also includes a large electronic medical records study of more than 42 million subjects, as well as autopsy studies of patients who died months after being infected. With immediate access to data and samples from existing, diverse study populations, it is anticipated that researchers will be able to accelerate the timeline for this important research.

Resource and Data Sharing

In order to act quickly to understand and combat COVID-19, NIH facilitated collaborations between researchers by creating centers and hubs where resources, findings, and technology were shared.

In FY 2020, NIH issued a funding opportunity announcement, which provided an expedited funding mechanism as part of the RADx-rad initiative.[1545] Specifically, under this funding opportunity, NIH intended to fund a single cooperative agreement for a Data Coordination Center to serve as a communication center and data hub for RADx-rad awardees. NIH implemented the RADx Data Hub[1546] to coordinate, manage, and provide researchers with workspace and capabilities for algorithm and analytic tools that could address compelling scientific and public health questions. In FY 2021, NLM awarded one grant to support the RADx-rad Consortium Data and Coordination Center, which will use advanced data management approaches to coordinate a consortium of innovative COVID-19 diagnostic technology developers.

In addition to diagnostic technology development, NIH has invested in resources to support therapeutic strategies and resources. Collaborative research resources are critical for successful drug development and identification of drugs that can be repurposed for new uses. In August 2020, NHLBI launched the Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS), which brings together multiple existing clinical trials networks to quickly test therapies with the potential to slow or stop COVID-19 progression.[1547] As part of ACTIV, CONNECTS is conducting a series of clinical trials to evaluate the safety and effectiveness of anticoagulants (blood thinners) to treat adults with COVID-19.

[1544] https://www.ninds.nih.gov/news-events/press-releases/nih-builds-large-nationwide-study-population-tens-thousands-support-research-long-term-effects-covid
[1545] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-20-019.html
[1546] https://radx-hub.nih.gov/home
[1547] https://nhlbi-connects.org/

To share COVID-19-related drug repurposing data and experiments openly and quickly, NCATS created a new resource for scientists called the OpenData Portal.[1548] NCATS researchers developed the portal by using SARS-CoV-2-related assays to screen more than 10,000 compounds, including the NCATS Pharmaceutical Collection of nearly 3,000 approved drugs, for their activity against the virus. The scientific community can use the data for a variety of drug repurposing activities, allowing them to formulate and test hypotheses, prioritize research opportunities, and speed the search for effective therapies against SARS-CoV-2 and COVID-19. As SARS-CoV-2 mutated, the information available in the OpenData Portal quickly adapted, in collaboration with the ACTIV Tracking Resistance and Coronavirus Evolution Program,[1549,1550] to share curated in vitro therapeutic activity data on SARS-CoV-2 variants.

In addition, NCATS plays a pivotal role in the Antiviral Program for Pandemics (APP),[1551] a multi-agency initiative to develop safe and effective oral antivirals. Launched in June 2021, the initial priority for the APP is to develop treatments for SARS-CoV-2 and other coronaviruses, with the program expanding to address other virus families that have pandemic potential. As part of the APP, NIH will be a key partner to accelerate antiviral development through early discovery and preclinical development.

To further bolster principles of FAIR data (Findable, Accessible, Interoperable, and Reusable) during the COVID-19 pandemic, NIH also invested in developing CDEs, which help to standardize data collection to enhance research reproducibility and enable integration of data from multiple studies.[1552] The COVID CDE Coordinating Committee (4C) brings together more than a dozen NIH groups working on developing and implementing CDEs for COVID 19-related research.

After therapeutics are developed, it is critical that they reach the patients who need them. NCATS' CTSA program supports a national network of medical research institutions called hubs, which work together to improve the translational research process to get more treatments to more patients more quickly.[1553] These hubs are working with community partners on a wide range of initiatives to accelerate the discovery and delivery of COVID-19 treatments and vaccines to those who need them. They develop and disseminate community engagement tools and resources, and they work to educate researchers and communities. These efforts have made the hubs into trusted community partners, allowing them to pivot rapidly to address COVID-19 health disparities. For example, several CTSA programs worked with underserved populations to better understand vaccine hesitancy.[1554] Other CTSA programs worked to reduce barriers to vaccination by bringing pop-up vaccine sites to Latino/a/x neighborhoods in Virginia and developing a sensory-friendly vaccination clinic for people with neurodevelopmental disabilities.[1555]

[1548] https://ncats.nih.gov/expertise/covid19-open-data-portal
[1549] https://opendata.ncats.nih.gov/variant/summary
[1550] https://www.nih.gov/research-training/medical-research-initiatives/activ/tracking-resistance-coronavirus-evolution-trace
[1551] https://ncats.nih.gov/antivirals
[1552] https://nexus.od.nih.gov/all/2021/06/24/common-data-elements-increasing-fair-data-sharing/
[1553] https://ncats.nih.gov/ctsa/about
[1554] https://ncats.nih.gov/ctsa/projects/community-engagement-across-the-ctsa-program-consortium
[1555] https://ncats.nih.gov/ctsa/projects/community-engagement-at-CTSA-hubs-during-the-COVID-19-pandemic

In addition to sharing information on treatment research, NIH is supporting resources to further understand the impact of COVID-19 on the body. The COVID-19 Neuro Databank/Biobank (NeuroCOVID) is a resource of clinical information as well as biospecimens from people of all ages who have experienced neurological problems associated with SARS-CoV-2 infection.[1556] NeuroCOVID can be accessed by scientists for research studies on preventing, managing, and treating neurological complications associated with COVID-19. The database will provide insight into how COVID-19 affects the nervous system, and how common, or rare, such complications are. Data will be freely available to the research community and will enable scientists to examine COVID-related neurological outcomes related to women's health and the health disparities experienced by racial and ethnic groups.

EHRs are another source of patient data that can be used to understand the COVID-19 pandemic. In FY 2020, NCATS formed the National COVID Cohort Collaborative (N3C) and opened the N3C Data Enclave to researchers.[1557] The N3C was created to enable research on the anonymized and harmonized EHR data of COVID-19-positive patients. The N3C is now the largest collection of EHR data on COVID-19 patients in the U.S. These data are being used to better answer research questions, such as those related to the characteristics, progression, and spread of SARS-CoV-2, COVID-19, and long-COVID. The data are also being used to identify which COVID-19 treatments are effective and which populations are most vulnerable to SARS-CoV-2 and why. This resource is a partnership of CTSA's National Center for Data to Health[1558] and several CTSA Program institutions, as well as NIGMS' Institutional Development Award (IDeA) Program institutions.

Figure 33: NCATS and NIGMS Clinical Research Networks and their partners leveraging real world EHR data to research COVID-19. Credit: NIH

[1556] https://www.ninds.nih.gov/News-Events/News-and-Press-Releases/Press-Releases/NIH-launches-COVID-19-Neuro-Databank
[1557] https://ncats.nih.gov/n3c
[1558] https://cd2h.org/mission#:~:text=The%20CTSA%20National%20Center%20for,Awards%20(CTSA)%20Program%20community

Other researchers with existing longitudinal cohorts and survey samples have been developing and fielding new survey items that assess various COVID-19-specific domains, such as symptoms, knowledge and attitudes, adherence to various mitigation behaviors, and social and economic impacts. NIH created a repository of these survey sample items to reduce duplication of efforts in survey design across the biomedical and behavioral research enterprise.[1559] The NIH Disaster Research Response (DR2) website includes a list of COVID-19 surveys and the domains assessed in the surveys, and it provides a wide array of data collection tools and resources used in other public health emergencies and disasters. It offers researchers a repository of survey and other measurement tools that are applicable to the COVID-19 pandemic.[1560] Additionally, the PhenX Toolkit includes a list of COVID-19-related measurement protocols drawn from the surveys listed in DR2. The PhenX Toolkit also has a large collection of well-established and validated measurement protocols suitable to incorporate into studies involving COVID-19.[1561]

In FY 2020, NIBIB launched the Medical Imaging and Data Resource Center (MIDRC), a collaboration of leading medical imaging organizations, to respond to the COVID-19 pandemic. [1562,1563] MIDRC aims to develop a high-quality repository of COVID-19-related medical images and associated clinical data to foster and create medical image-based AI tools for use in the detection, diagnosis, prognosis, and monitoring of COVID-19. NLM researchers also developed COVID-19-CT-CXR, a public database of COVID-19 chest X-ray and CT images, which are automatically extracted from COVID-19-relevant articles from NLM's PubMed Central Open Access Subset.[1564]

NLM's pandemic response repurposed or extended existing research resources for public health purposes and supported the response to the COVID-19 pandemic by making new data and information related to COVID-19 readily available. NLM collaborated with more than 50 publishers and scholarly societies to provide free and immediate public access to all coronavirus-related publications and associated data via PMC as part of its Public Health Emergency COVID-19 Initiative.[1565,1566] Through 2021, there were 210,000 articles collected under this Initiative, which had been viewed 275 million times. NLM also developed LitCovid, which uses natural language processing methods (a type of AI) to help classify COVID-19 research publications as relating to prevention, diagnosis, treatment, and other categories. [1567]

Research findings usually undergo peer-review prior to being published in scientific journals, which can be a long and laborious process. To share novel research findings on SARS-CoV-2 and COVID-19 as quickly as possible, many scientists shared their research findings in preprint archives, which are online repositories of research articles that have not yet been peer-reviewed. To enable researchers to explore

[1559] https://obssr.od.nih.gov/news-and-events/news/covid-19-specific-survey-items-now-available-on-phenx-and-the-nih-disaster-research-response-dr2-platforms
[1560] https://tools.niehs.nih.gov/dr2/
[1561] https://www.phenxtoolkit.org/index.php
[1562] https://www.nibib.nih.gov/medical-imaging-and-data-resource-center
[1563] https://www.midrc.org/
[1564] Peng Y, et al. *IEEE Trans Big Data*. 2021 Mar 1;7(1):3-12. PMID: 33997112.
[1565] https://www.nih.gov/news-events/news-releases/national-library-medicine-expands-access-coronavirus-literature-through-pubmed-central
[1566] https://www.ncbi.nlm.nih.gov/pmc/about/covid-19/
[1567] Chen Q, et al. *Nucleic Acids Res*. 2021 Jan 8;49(D1):D1534-D1540. PMID: 33166392.

and analyze the rapidly growing set of advances in COVID-19 research as they accumulated in real time, NIH's Office of Portfolio Analysis developed the COVID-19 Portfolio Tool, a comprehensive, expert-curated portfolio of COVID-19 publications and preprints.[1568] This tool is updated daily with the latest available data, and it complements efforts by NLM to aggregate full-text documents that are broadly related to COVID-19.

NLM launched the NIH Preprint Pilot in June 2020, which increased access to the results of NIH-funded COVID-related scientific research. By the end of FY 2021, it had made more than 2,700 preprints reporting NIH-funded COVID-19 research publicly available in the PMC archive of full-text biomedical literature, which was further discoverable in PubMed database of citations to biomedical literature.[1569] Through the pilot, NLM ensured broad discovery of publicly available research results as early as possible, helped maximized the impact of NIH funding, and accelerated the point at which this research would otherwise be discoverable in PMC and PubMed, supporting the NIH response to the ongoing public health emergency.[1570]

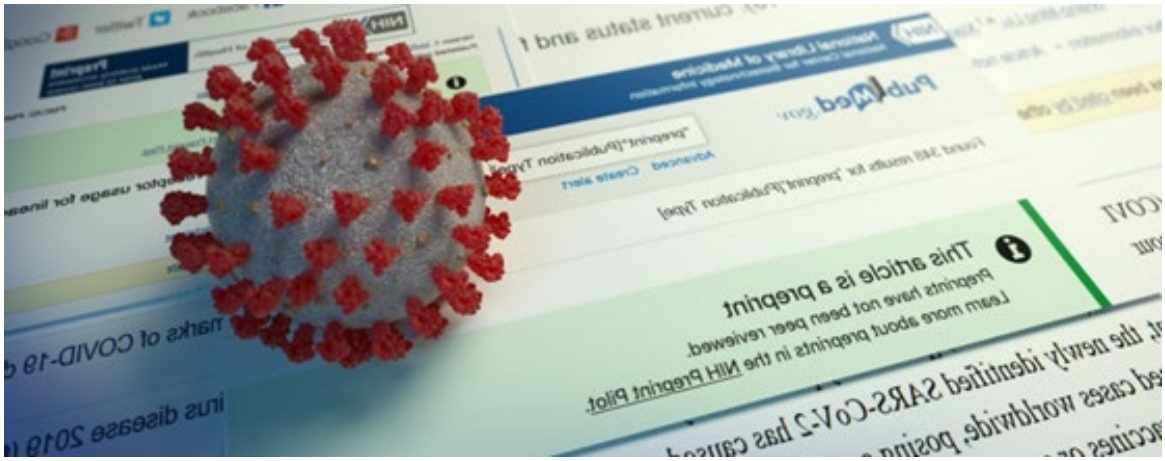


Figure 34: The NIH Preprint Pilot is adding preprints reporting on results of NIH-funded research to PMC and making them discoverable in PubMed. Credit: NLM OCPL

Community Engagement and Communication

In addition to supporting researchers by providing resources and infrastructure for collaboration and data sharing, NIH is supporting efforts to directly reach communities impacted by the COVID-19 pandemic and create an archive to document the broad impacts of the pandemic and other disease outbreaks.

In the U.S., COVID-19 has taken its toll on almost every community, but some groups—especially Black/African Americans, Hispanic/Latinos, and American Indian/Alaska Natives—have had increased rates of infection, hospitalization, and deaths compared with Whites. Building on its established history of engaging communities in research, NIH developed the Community Engagement Alliance (CEAL) Against

[1568] https://icite.od.nih.gov/covid19/search/
[1569] https://www.ncbi.nlm.nih.gov/pmc/about/nihpreprints/
[1570] https://nlmdirector.nlm.nih.gov/2020/06/09/the-nih-preprint-pilot-a-new-experiment-for-a-new-era/

COVID-19 Disparities.[1571] This initiative connects researchers to trusted leaders and organizations in those communities hardest hit by COVID-19, helping them work together to address misinformation, increase the use of practices to prevent spread of the virus, and ensure that clinical trials include people in these communities, so that the treatments and vaccines developed will work for everyone. CEAL is led by NIMHD and NHLBI.[1572] NLM leveraged its Network of the National Library of Medicine (NNLM) in support of CEAL. Through its more than 8,800 participating organizations, NNLM is supporting COVID-19 community awareness and engagement via outreach activities about long-term research and clinical trials support. NLM's Spanish language videos that were created to support CEAL are among the most popular NLM YouTube content.

Figure 35: The Community Engagement Alliance (CEAL) Against COVID-19 Disparities works closely with the communities hit hardest by COVID-19. Credit: NIH Community Engagement Alliance

NIH has also supported government-wide communications about the COVID-19 pandemic. The NIH Office of Communications and Public Liaison has played a central role in the U.S. government's efforts to develop, coordinate, and communicate important health information to the American public. This includes: launching a central website about NIH's COVID-19 research,[1573] supporting major announcements on NIH COVID-19 research efforts for vaccine, treatment, and testing initiatives,[1574] responding to a high volume of media interview requests about the pandemic and ensuring NIH spokespeople reached a range of audiences through a variety of national and local media outlets, ensuring clear and coordinated messaging to external and internal audiences about the latest data-backed mitigation measures, developing COVID-19 content for NIH social media platforms, and planning and promoting public COVID-19 vaccination events. Additionally, NIEHS has developed a curriculum designed to guide high school students (grades 9-12) as they explore various risk factors involved in COVID-19 spread and its resulting mortality, including biological, socio-economic, and environmental factors.[1575]

[1571] https://covid19community.nih.gov/
[1572] https://www.nlm.nih.gov/oet/ed/ceal/index.html
[1573] https://covid19.nih.gov/
[1574] https://covid19.nih.gov/news-and-stories#news-from-across-nih-1
[1575] https://www.niehs.nih.gov/health/scied/teachers/covid-19/index.cfm

Figure 36: NIH COVID-19 vaccination event. Dr. Anthony Fauci, NIAID Director, gives the thumbs up sign after receiving the COVID-19 vaccine at the HHS/NIH COVID-19 Vaccine Kick-Off event at NIH on 12/22/20. Credit: NIH

NLM curates and makes publicly available collections of web-based materials related to health and medicine.[1576,1577] NLM selects websites and social media that document government and non-government responses, news, and perspectives of those who experience key health events first-hand as patients, victims, or caregivers, and/or political debates surrounding the health events. Collections include content documenting the opioid epidemic, H7N9 avian flu, Autism spectrum disorder, Alzheimer's disease, HIV/AIDS, and the 2014 Ebola outbreak. More recently, NLM has been documenting the COVID-19 pandemic. NLM is also contributing to collecting COVID-19-related content that is maintained by the International Internet Preservation Consortium Novel Coronavirus outbreak web archive collection.

Understanding the Immune System and Environmental Health

A recent study by NIAID researchers found that memory T cells, which are located throughout the body and are required to maintain immune responses to infectious agents, retreat to the bone marrow during dietary restriction. The study in mice found that animals undergoing dietary restriction were better protected against tumors and bacterial infections than animals with unrestricted diets.[1578] Mice with restricted diets had more robust memory T cell responses and were better protected from illness. The researchers repeated this experiment using a vaccine that trains immune cells to fight melanomas and found that memory T cells were more protective against tumors in mice receiving less food, which suggests that the immune system evolved to withstand food scarcity.

[1576] Speaker SL, et al. *J Med Libr Assoc*. 2020 Oct 1;108(4):656-662. PMID: 33013228.
[1577] https://circulatingnow.nlm.nih.gov/2021/05/13/exploring-the-data-of-web-archives-as-part-of-data-science-nlm/
[1578] https://www.niaid.nih.gov/news-events/memory-t-cells-shelter-bone-marrow-boosting-immunity-mice-restricted-diets

During FY 2019–2021, NIH brought together experts in infectious disease, global public health, toxicology, environmental epidemiology, and science policy to explore the growing body of research on the links between environmental stressors, infectious disease, and human health.[1579] A series of workshops investigated how emerging environmental exposure assessment tools could help identify and monitor critical pathways for exposure to infectious agents, and how recent advances in climate and environmental health modeling techniques could be applied to predict transmission dynamics and provide early warning of emerging infectious disease outbreaks.[1580]

In FY 2021, four awards were granted as part of the joint NIEHS-NSF initiative, the Centers for Oceans and Human Health 3: Impacts of Climate Change on Oceans and Great Lakes.[1581] The focus of the program is to support research on the emerging exposures, toxicities, and human health impacts that arise in these environments and how climate change is influencing these factors now and in the future.

Public Health Emergency Preparedness

Public health emergencies arise when unexpected incidents, both natural and man-made, have the potential to significantly influence the health of citizens, necessitating a rapid and robust response. HHS is a national leader in responding to such incidents, and many agencies within HHS have critical roles in ensuring an appropriate response to public health emergencies.

Summary of NIH Activities

NIH's commitment to disaster resilience and public health is founded on more than three decades of research. Multiple NIH ICs and grantees conduct research focusing on disaster preparedness, response, and recovery, which provides critical information when disasters strike. NIH also supports research to address public health issues arising from natural and man-made disasters; biological, chemical, and radiological threats; epidemics; and other environmental factors. NIH supports programs to help respond to public health emergencies in general, as well as to specific types of incidents. Examples of current efforts are highlighted below.

Additional NIH efforts to understand and respond to infectious diseases are highlighted in the Infectious Diseases and Biodefense section above**.**

Emergency Preparedness Across NIH

NICHD researchers analyzed data from the Consecutive Pregnancies Study, which included 50,000 women at 20 hospitals in Utah and Idaho. Using data from the U.S. Environmental Protection Agency and other sources, they estimated the women's exposure to air pollutants at different time points. Results suggest that exposure to high levels of certain common air pollutants in early pregnancy may increase the risk of pregnancy-induced high blood pressure. In addition, the results suggested that exposure to a class of air

[1579] https://www.nationalacademies.org/event/01-15-2019/understanding-the-interplay-of-environmental-stressors-infectious-disease-and-human-health-a-workshop
[1580] https://www.nationalacademies.org/event/06-08-2021/pivotal-interfaces-of-environmental-health-and-infectious-disease-research-to-inform-responses-to-outbreaks-epidemics-and-pandemics-a-workshop
[1581] https://www.niehs.nih.gov/research/supported/centers/oceans/grantees/index.cfm

pollutants known as volatile organic compounds in mid-pregnancy may increase the risk for preeclampsia, a potentially fatal disorder of pregnancy affecting blood pressure and kidney function.[1582,1583]

NIAID-funded research has expanded the toolbox of medical countermeasures available when a catastrophic event exposes people to high doses of radiation. In January 2021, FDA approved the use of romiplostim (trade name Nplate) to increase survival of adults and children, including newborns, who are acutely exposed to high doses of radiation that damage the bone marrow.[1584] The approval of romiplostim is the result of a collaboration between NIAID, BARDA, and Amgen, the biotechnology company that manufactures the drug. The FDA's decision was based largely on NIAID-supported studies showing that romiplostim greatly increases survival in an animal model of radiation exposure.[1585,1586]

In recent years, approximately 40,000 deaths each year in the U.S. are from firearms, 60 percent of which are suicides and 37 percent of which are homicides.[1587] In 2019, firearm-related injuries were one of the leading causes of death for American children, teens, and adults younger than 65. In addition to firearm deaths, many more Americans experience non-fatal firearm injuries. When firearms are involved with violent events, the risk for injury and mortality increases. Firearm violence is responsible for three quarters of all homicide deaths and is the most common and lethal means of suicide. Firearm injury and mortality also contribute to health disparities, with some demographic groups being at much higher risk than others. In 2019, Black males between the ages of 15 and 24 had a gun homicide rate more than 20 times higher than White males of the same age group.[1588] The Office of Behavioral and Social Sciences Research (OBSSR) coordinates firearm injury and mortality prevention research across the NIH in collaboration with a number of ICOs.

NIH is committed to supporting scientific research to develop, evaluate, and implement effective public health interventions to understand and prevent violence, including firearm violence, and the resulting trauma, injuries, and mortality. NIH supported a total of $14 million in FY 2020 and $19 million in FY 2021 in Firearms Research. [1589] This included $2.5 million in funding provided through the FY 2020 *Further Consolidated Appropriations Act* (P.L. 116-94) and the FY 2021 *Consolidated Appropriations Act* (P.L. 116-260) to conduct research on firearm injury and mortality prevention. In response to this appropriation, NIH released two FOAs in each of those years (PAR-20-143,[1590] NOT-OD-20-089,[1591] PAR-21-191,[1592] and PAR-21-192[1593]). These FOAs were intended to solicit applications for research to improve understanding of the determinants of firearm injury, the identification of those at risk of firearm injury (including both

[1582] https://www.nichd.nih.gov/newsroom/news/082319-pregnancy-related-blood-pressure
[1583] Nobles CJ, et al. *Hypertension.* 2019 Aug;74(2):384-390. PMID: 31230552.
[1584] https://www.niaid.nih.gov/news-events/niaid-funded-research-leads-approval-drug-acute-radiation-injury
[1585] Wong K, et al. *Int J Radiat Biol* 2020 Jan;96(1):155-166. PMID: 31216213.
[1586] Bunin DI, et al. *Int J Radiat Biol* 2020 Jan;96(1):145-154. PMID: 31021662.
[1587] https://www.cdc.gov/nchs/fastats/injury.htm
[1588] https://www.cdc.gov/vitalsigns/firearm-deaths/index.html
[1589] https://report.nih.gov/funding/categorical-spending#/
[1590] https://grants.nih.gov/grants/guide/pa-files/PAR-20-143.html
[1591] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-089.html
[1592] https://grants.nih.gov/grants/guide/pa-files/PAR-21-191.html
[1593] https://grants.nih.gov/grants/guide/pa-files/PAR-21-192.html

victims and perpetrators), the development and evaluation of innovative interventions to prevent firearm injury and mortality, and the examination of approaches to improve the implementation of existing, evidence-based interventions to prevent firearm injury and mortality. The FOAs took a broad public health approach to firearm injury and mortality prevention, encouraging research on interventions delivered by healthcare providers and systems and on those delivered in community settings, as well as research that integrated individual, family, interpersonal, community, and structural or system (e.g., criminal justice, schools, hospital systems) approaches to firearm injury and mortality prevention.

The FOAs were published in March 2020[1594] and 2021.[1595] While the U.S. Government and research institutions pivoted to research to control the spread of, treat, and prevent SARS-CoV-2 and COVID-19, there was a good response to these FOAs, and NIH was able to support nine awards in 2020 and ten awards in 2021. These awards built upon the existing NIH violence research portfolio and address gaps and emerging opportunities to understand and prevent firearm violence, injury, and mortality. Several projects sought to identify risk and protective factors, some sought to consider real-world barrier and facilitators to support broader adoption of safe practices, some addressed suicide, intimate partner violence, and youth violence, and some projects were diverse in their inclusion of populations from youth to older adults, Alaska Native populations, men and women, and those who are or are not firearm owners. In 2021, to supplement the appropriated funds, the NIA Alzheimer's Disease and Related Disorders program partially funded one of the awards and fully funded an additional grant award addressing firearm safety among older adults with mild cognitive impairment and early dementia. All ten awards build upon the existing NIH violence research portfolio and address gaps and emerging opportunities to understand and prevent firearm violence injury and mortality.[1596,1597]

Disasters and public health emergencies—whether local or global, natural or human-caused—result in unique combinations of human exposures, hazards, and stressors. These conditions are often not well understood in terms of their immediate physical and mental health impacts, or their longer-term consequences. NIEHS coordinates the Disaster Research Response (DR2) program, which leads U.S. efforts and works with global partners to improve capacity for timely research related to disasters and public health emergencies. The DR2 Program provides a repository of data collection tools and related resources that are curated to empower human health research in response to disasters and public health emergencies. The repository includes more than 200 keywords and houses the COVID-19 Collection of Research Tools.[1598]

[1594] https://grants.nih.gov/grants/guide/pa-files/PAR-20-143.html
[1595] https://grants.nih.gov/grants/guide/pa-files/PAR-21-192.html
[1596] https://obssr.od.nih.gov/news-and-events/news/nih-awards-grants-firearm-injury-and-mortality-prevention-research
[1597] https://obssr.od.nih.gov/news-and-events/news/director-voice/nih-awards-10-grants-addressing-firearm-violence-prevention
[1598] https://tools.niehs.nih.gov/dr2/

Rare and Undiagnosed Diseases

A rare disease is defined as one that affects fewer than 200,000 people and may involve chronic illness, disability, and premature death.[1599] Although such diseases are individually rare, collectively, an estimated 25 to 30 million Americans are affected—that is one in ten people.[1600] Rare diseases are often devastating and costly for patients, their families, and the nation, largely due to the severity of these conditions and because the diagnosis frequently occurs long after the symptoms have appeared. Moreover, treatment is often unavailable, even after a disease is diagnosed, because it would require developing treatments for small, geographically dispersed populations. Of the 7,000 identified rare and neglected diseases for which we know the molecular cause, only about 500 have approved treatments.[1601]

Summary of NIH Activities

NIH funding for rare diseases was $5,655 million in FY 2019, $5,947 million in FY 2020, and $6,191 million in FY 2021. Since rare and undiagnosed diseases can impact any organ system, funded research and activities are conducted throughout NIH, and several of NIH's activities in this area are presented in this section. Additional work relating to rare and undiagnosed diseases, as they pertain to specific health areas, are illustrated in other sections of this chapter, as appropriate.

Undiagnosed Diseases

Identifying an underlying diagnosis for many conditions can be a long and frustrating experience. Individuals with rare conditions can go for extended periods without a diagnosis. These types of rare disorders are referred to as undiagnosed diseases. Such diseases are difficult for doctors to diagnose because they are rare, have not previously been described, or are unrecognized forms of more common diseases. Multiple efforts at NIH aim to provide answers to patients with mysterious conditions that have long eluded diagnosis, while also advancing medical knowledge about rare and common diseases.

A study by the NIH Common Fund's Undiagnosed Diseases Network (UDN),[1602] which aims to improve the diagnosis of rare and undiagnosed conditions, indicates that a personalized approach to clinical care leads to diagnoses for previously undiagnosed cases. In this study, which was also supported by NHGRI and NINDS, researchers analyzed data from four UDN clinical sites from 2015 to 2019 to assess the number of diagnoses, new disease gene discoveries, and underlying investigative methods required to make the diagnoses. The study showed that 65 percent of diagnoses were made due to the UDN's unique diagnostic and research paradigms, which surpass standard diagnostic processes.[1603,1604,1605]

In another study, NIH-supported researchers led an international team toward the discovery of a new, adult-onset inflammatory disease called VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory,

---

[1599] https://www.ncbi.nlm.nih.gov/medgen/146261#Definition
[1600] https://ncats.nih.gov/files/NCATS_RareDiseasesFactSheet.pdf
[1601] https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/rare-diseases
[1602] https://commonfund.nih.gov/Diseases
[1603] https://commonfund.nih.gov/diseases/highlights
[1604] https://corporate.dukehealth.org/news/diagnoses-rare-diseases-enhanced-through-teamwork-national-network
[1605] Schoch K et al. Genet Med 2021;23(2):259-271. PMID: 33093671.

somatic) syndrome.[1606] Middle-aged men with this condition do not respond well to therapy and are at increased risk for early death. The scientists found that the disorder is caused by a mutation in the *UBA1* gene, which provides instructions for making the ubiquitin-activating enzyme E1 and is located on the X chromosome. This study highlights the potential of using a genome-first approach to help doctors evaluate and treat inflammatory diseases, a strategy that may be useful for rheumatic diseases that affect the bone, joint, and muscle. Such diseases are often difficult to diagnose due to the complexity and variety of signs and symptoms associated with these conditions.

Rare Diseases

There are unique challenges for researchers studying rare diseases, ranging from addressing the large number of rare disorders and the complexity of each disease, to the small patient populations, to the limited availability of data. There are unique challenges in optimizing study design, patient recruitment, and patient retention. For these reasons, NIH promotes multiple efforts to help the biomedical research community advance our understanding of the underlying disease mechanisms of rare diseases and to develop potential therapeutics. Several of these advances are discussed below.

Rare Disease Day® takes place worldwide on (or near) the last day of February each year. The goal of the event is to raise awareness among policymakers and the public about rare diseases and the impact of those conditions on patients' lives. As part of this global annual observance, NCATS and the NIH CC sponsor "Rare Disease Day at NIH," which aims to raise awareness about rare diseases, the people they affect, and the NIH collaborations that address scientific challenges and advance research for new treatments. Rare Disease Day at NIH provides an opportunity for patients, patient organizations, health care providers, regulators, researchers, and others, to forge connections, share stories and learn from one another. Co-sponsored by NCATS and the NIH CC, the event features discussions of rare diseases and the people they affect. It also highlights the NIH research collaborations that are underway that address scientific challenges and advance new treatments.[1607]

[1606] Beck DB et al. N Eng J Med 2020;383(27):2628-2638. PMID: 33108101.
[1607] https://ncats.nih.gov/events/rdd/past-events

Figure 37: The IDeaS Initiative: Pilot Study to Assess the Impact of Rare Diseases on Patients and Healthcare Systems. Credit: The IDeaS Initiative, NIH

One of the big challenges that those with a rare disease face is the associated health care costs, which to-date have been underestimated. A new, retrospective study of medical and insurance records indicates health care costs for someone with a rare disease are three to five times greater than the costs for someone without a rare disease. The study, led by NCATS, is called the IDeaS (Impact of Rare Diseases on Patients and Healthcare Systems) Initiative. It provides new evidence of the potential impact of rare diseases on public health, suggesting that nationwide medical costs for individuals with rare diseases are on par with those costs for cancer and heart failure.[1608,1609] A summary of this study and other recent independent studies by NCATS, the EveryLife Foundation, and the U.S. GAO, indicates that the total direct and indirect costs of rare diseases in the U.S. are likely more than $1 trillion.[1610] The findings underscore an urgent need for more research, as well as earlier and more accurate diagnoses of and interventions for these disorders.

In 2021, NHGRI launched the Genomics Research Elucidates Genetics of Rare Disease (GREGoR) Consortium, which will be supported by nearly $80 million over five years to help researchers identify the genetic causes of rare genetic diseases that have eluded complete characterization (including identifying the causative gene). The GREGoR Consortium is aimed at significantly increasing the proportion of Mendelian disorders (disorders characterized by a mutation in single gene) with an identified genetic cause, through enhanced data sharing, collaboration, and an increased focus on the application of new technologies, sequencing strategies, and analytical approaches. The program comprises five research

[1608] https://ncats.nih.gov/news/releases/2021/nih-study-suggests-people-with-rare-diseases-face-significantly-higher-health-care-costs
[1609] Tisdale A et al. Orphanet J Rare Dis 2021;16(1):429. PMID:34674728.
[1610] https://www.healthaffairs.org/do/10.1377/forefront.20220128.987667

centers and a data coordinating center. The research centers will sequence samples from patients with Mendelian conditions and develop and apply novel approaches to discover causal variants. The centers will also aim to solve "unsolved" cases, for which a candidate gene was not identified, by using only whole exome sequencing. The data coordinating center will manage data release and disseminate findings, coordinate program logistics and administrative duties, and oversee an "opportunity fund" for follow-up functional studies of discoveries made by the GREGoR Consortium research centers.[1611]

Many rare diseases have a genetic cause, which means that understanding of the underlying genetic basis is key to diagnosis and treatment. Evolving from NIH's participation in the International Human Genome Sequencing Project, the NHGRI Genome Sequencing Program (GSP) works to discover the genomic bases of rare and common diseases. The GSP includes both the Centers for Common Disease Genomics, where researchers identify genomic variants that either increase or decrease risk associated with common diseases, and the Centers for Mendelian Genomics, where researchers discover the genomic bases for rare Mendelian diseases. The GSP also develops methods, tools, and knowledge, which are made available to the biomedical research community. NHGRI has committed to provide support for three to five additional Centers for Mendelian Genomics over the next five years.[1612,1613,1614]

NICHD IRP researchers have identified additional symptoms of EPAS1 gain-of-function syndrome, a rare disease resulting in hormone-secreting tumors and an increase in red blood cells. In a group of nine patients, and in a mouse model of the disease developed by researchers, malformations of blood vessels and related structures were observed in the eyes, brain, neck, and spine. The disease results from a mutation in the *EPAS1* gene, which disrupts the function of its corresponding protein, hypoxia-inducible factor-2a (HIF-2a). This rare disease provides an opportunity to better understand the role of HIF-2a, which is involved in normal development, blood vessel formation, immune responses and inflammation, and the development of tumors, which usually have lower levels of oxygen compared with surrounding tissue.[1615]

[1611] https://www.genome.gov/Funded-Programs-Projects/GREGOR-Consortium
[1612] https://www.genome.gov/Funded-Programs-Projects/NHGRI-Genome-Sequencing-Program
[1613] http://www.mendelian.org/
[1614] https://ccdg.rutgers.edu/
[1615] https://www.nichd.nih.gov/newsroom/news/031521-EPAS1

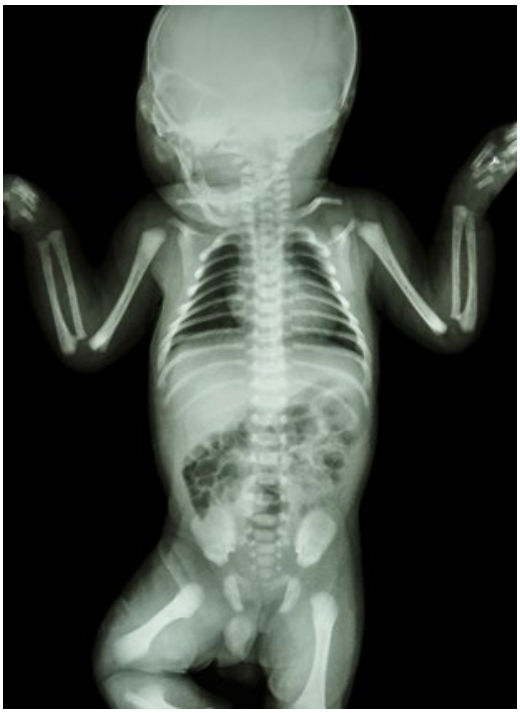


Figure 38: X-ray of a healthy infant skeleton. Credit: iStock

Another team of researchers, supported by NIAMS, that specializes in skeletal conditions with unknown genetic causes, are investigating a gain-of-function mutation that leads to skeletal dysplasia. They identified a mutation in a microRNA molecule that bestows new functions on the molecule in addition to knocking out its original functions (i.e., a neomorphic effect).[1616] This is the first time a neomorphic mutation has been identified as the basis for a human genetic skeletal disease. The discovery expands our current understanding of how mutations in microRNAs contribute to human disease development. This is important for patients with this form of skeletal dysplasia and other conditions potentially caused by similar mechanisms, but it also has broader implications for scientific investigations into the function of microRNA and other regulatory RNAs. This research, and the studies described above, illustrate that in many instances, research into the mechanisms underlying a rare disease provide valuable insight that can also be applied to understanding both normal processes in the body and common diseases.

Another team of NIAMS-supported researchers identified a mutation for rare bone disease, which has provided valuable insight into the way that bone forms. Melorheostosis is a rare disease that causes increased bone formation, usually in one arm or leg. Researchers examined a cohort of fifteen patients with melorheostosis and found that four had a mutation in the same gene, *SMAD3*.[1617] The mutation was only observed in the osteoblasts of bone affected by the disease, not in the rest of the body. These findings point to a possible mechanism for the exuberant bone formation seen in these patients, while shedding light on the ways new bone can be formed in adults and highlighting possible future treatment targets.

[1616] Grigelioniene, G et al. Nat Med 2019;25(4):583-590. PMID: 30804514.
[1617] Kang H et al. J Exp Med 2020;217(5):e20191499. PMID: 32232430.

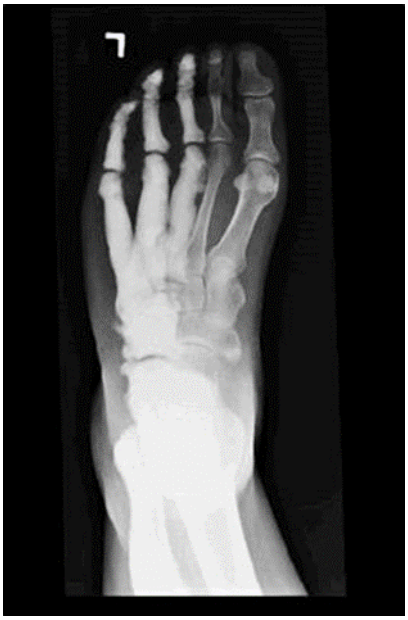


Figure 39: X-ray showing excess bone formation in the foot, ankle, and lower leg of a patient with melorheostosis. Credit: Dr. Timothy Bhattacharyya, NIAMS

The rare disease juvenile dermatomyositis (JDM) is a chronic autoimmune inflammatory disease[1618] that begins in childhood and causes muscle inflammation and a skin rash. While some patients respond to standard anti-inflammatory therapies, such as corticosteroids, two-thirds do not respond, and novel interventions are needed for these individuals. Based on foundational studies to better understand how the immune system overreacts in this disease, NIAMS clinicians planned a compassionate-use clinical study to see if the Janus Kinase inhibitor, baricitinib, could help children with chronic, treatment-resistant JDM. All participants in the study responded to the treatment and showed improvement in skin rash and/or muscle strength and inflammation, and their response has been sustained for more than a year while other immunosuppressive medications were tapered or discontinued.

Identification of a rare disease in a patient is a vital step to treatment and management. However, the diagnostic delay compared with diagnosis of more common disorders can be significant. Development of diagnostic tests to screen newborns for rare genetic disorders is particularly important because early identification can result in early intervention. One recent NIH-supported success is the first FDA-authorized newborn screening platform for lysosomal storage disorders. Small-business funding from NICHD enabled a company to develop and commercialize a platform that uses innovative digital microfluidics technology to quickly test for four lysosomal storage disorders: mucopolysaccharidosis type I, Pompe disease, Gaucher disease, and Fabry disease. In early 2021, the company announced a milestone, delivering ten million newborn screening tests in the U.S. and other countries.[1619]

NIH Clinical and Translational Science Awards (CTSA) program investigators have been collaborating to enhance newborn screening by conducting research to gather evidence to support the inclusion of fragile

[1618] Kim H et al. Ann Rheum Dis 2021;80(3):406-408. PMID: 32843325.
[1619] https://www.nichd.nih.gov/grants-contracts/SBIR_STTR/showcase/SEEKER

X syndrome and other rare genetic diseases in standard newborn screenings. NCATS, along with NICHD, supports the CTSA Early Check research study, which launched in October 2018 in North Carolina and offers free newborn/infant screening tests for genetic disorders or medical conditions that are not included in the state's standard newborn screening.[1620] In one study, Early Check tested nearly 14,000 newborns born in North Carolina and identified three babies with Spinal Muscular Atrophy (SMA), a genetic condition that causes progressive muscle weakness and in severe cases leads to death around age two or three. As a result of being identified as having the condition while still a newborn, one of the babies is now receiving a newly approved gene therapy. Receiving treatment as early as possible has been shown to lead to better health outcomes in children with SMA.[1621]

For many individuals with a rare disease, early identification leads to the possibility of early intervention. However, only about ten percent of rare diseases have an FDA-approved therapy or treatment.[1622] NIH is committed to supporting the development of new treatments for a wide range of rare disorders. An NCATS-led analysis found that orphan-designated drugs for rare diseases spent, on average, 552 more days in clinical development than a typical drug. At a one-disease-at-a-time pace, it will take thousands of years to tackle all rare diseases. To increase the number of new treatments quickly, therapeutic approaches that work for multiple diseases are needed. NCATS' preclinical efforts include finding and developing already-approved drugs that could treat additional diseases.[1623,1624]

The NCATS Therapeutics for Rare and Neglected Diseases (TRND) program de-risks promising preclinical therapeutic candidates to foster clinical development, and to ultimately deliver these much-needed treatments to patients. Four such prior collaborations have recently reached major regulatory milestones. Mycovia Pharmaceuticals received FDA approval for an antifungal drug produced using a TRND-developed manufacturing process,[1625] and the pharmaceutical company PTC Therapeutics is in the latter stages of a marketing authorization application process with the European Medicines Agency for an AADC deficiency gene therapy.[1626] In addition, ReveraGen BioPharma and the Drugs for Neglected Diseases initiative are both moving towards approval for treatments for Duchenne muscular dystrophy[1627] and human African tryponosomiasis (also known as "sleeping sickness"), respectively.[1628]

Recent TRND research has led to a phase 1 clinical trial testing of a drug approved abroad for Parkinson's disease as a treatment for two closely related rare blood disorders: beta-thalassemia and sickle cell disease. These hemoglobin disorders, called hemoglobinopathies, can result in moderate-to-severe anemia, with symptoms ranging from weakness and fatigue to damage to the heart, brain, lungs, and other organs. No drugs are approved to treat the underlying causes of these disorders. Although both are

[1620] Bailey DB et al. PubMed 2019;Jul 17. PMID: 31315600.
[1621] https://www.rti.org/news/three-babies-spinal-muscular-atrophy-have-bright-futures-early-check
[1622] https://ncats.nih.gov/news/releases/2021/nih-study-suggests-people-with-rare-diseases-face-significantly-higher-health-care-costs
[1623] Brown DG et al. Nat Rev Drug Discov 2021;Nov 10. Epub ahead of print. PMID: 34759309.
[1624] Rosenblum JS et al. JCI Insight 2021;6(5):e144368. PMID: 33497361.
[1625] https://ncats.nih.gov/trnd/projects/complete/antifungal-vt1129-cryptococcal-meningitis
[1626] https://ncats.nih.gov/trnd/projects/complete/aadc-deficiency
[1627] https://ncats.nih.gov/trnd/projects/complete/vbp15-duchenne-muscular-dystrophy
[1628] https://ncats.nih.gov/trnd/projects/active/acoziborole-human-african-trypanosomiasis

orphan conditions in the U.S., beta-thalassemia and sickle cell disease affect millions of people worldwide, are increasing in frequency in the U.S., and are classified by the World Health Organization as a growing global health burden.[1629,1630]

In October 2021, NCATS launched the Bespoke Gene Therapy Consortium (BGTC) as part of the Accelerating Medicines Partnership® (AMP®) program, a public-private partnership among NIH, FDA, multiple pharmaceutical and life sciences companies, and nonprofit and other organizations. The BGTC is establishing platforms and standards to speed the development and delivery of customized or *bespoke* gene therapies that could treat millions of people affected by rare diseases, including diseases that are too rare to be of commercial interest. The BGTC will generate gene therapy resources that the research community can use to streamline gene therapy development for rare disorders, making the process more efficient and less costly. NCATS IRP laboratories will play an important role in the BGTC's basic biology component. With expertise in preclinical drug development—including assay development, high-throughput screening, disease modeling, toxicity testing, and more—NCATS researchers are poised to generate data that could lead to improved vector production and therapeutic gene activity. A clinical component of BGTC-funded research will support between four and six clinical trials, each focused on a different rare disease. The BGTC also will explore methods to streamline regulatory requirements and processes for FDA approval of safe and effective gene therapies, including developing standardized approaches to preclinical testing (e.g., toxicology studies).[1631]

Cell and animal models can provide an important tool in the search for new treatments for rare diseases. Researchers supported by the NIH Common Fund's Somatic Cell Genome Editing program, in collaboration with NHGRI used a genome editing tool that specifically targeted and corrected the disease-causing gene in Hutchinson-Gilford progeria syndrome (HGPS), a rare disease that induces rapid aging and shortens lifespan. The delivery of this tool into lab-grown cells from HGPS patients resulted in 90 percent of the cells containing the edited gene and a significant reduction in cellular abnormalities. A single use of the tool in a mouse model of HGPS greatly extended lifespan, from 215 to 510 days. Improved health in the aorta was also observed in the hearts of treated mice, which was particularly encouraging because deterioration of the aorta is a major contributor to disease and death in children with HGPS.[1632,1633,1634]

Additional research supported by the NIH Common Fund's Somatic Cell Genome Editing program has demonstrated that gene editing technology shows promise for treatments targeting other rare diseases. Research supported in part by the Somatic Cell Genome Editing program, in collaboration with NCATS, developed a gene editing method (referred to as prime editing) that could, in principle, correct up to 89 percent of known genetic variants associated with human diseases. Prime editing does not require

---

[1629] https://ncats.nih.gov/trnd/projects/complete/pb04-hemoglobinopathies
[1630] https://clinicaltrials.gov/ct2/show/NCT04432623
[1631] https://ncats.nih.gov/programs/BGTC, https://ncats.nih.gov/news/releases/2021/nih-fda-and-15-private-organizations-join-forces-to-increase-effective-gene-therapies-for-rare-diseases
[1632] https://commonfund.nih.gov/editing/highlights#progeria
[1633] https://www.genome.gov/news/news-release/DNA-editing-method-shows-promise-to-treat-mouse-model-of-progeria
[1634] Koblan LW et al. Nature 2021;589(7843):608-614. PMID: 33408413.

double-strand breaks of DNA or donor DNA templates, so this process provides a new search-and-replace capability that substantially expands the scope of genome editing.[1635]

The NCATS Platform Vector Gene Therapy (PaVe-GT) program, conducted in collaboration with NINDS and NHGRI, is testing whether it is possible to develop a standard set of gene therapy tools that researchers everywhere can use to create treatments for a range of rare diseases. PaVe-GT researchers are using a common gene delivery vehicle, adeno-associated virus, and uniform manufacturing methods. The therapeutic targets are four rare genetic diseases: two inherited muscle weakness/neuromuscular junction disorders and two inherited metabolic diseases. If successful, this technology can be adapted to many other rare diseases, decreasing the cost and time necessary to develop treatments.[1636]

Gene-targeted therapies have the potential to provide treatments for multiple disorders rapidly. For example, recently discovered gene editing approaches can, in principle, correct approximately 90 percent of all human disease-causing mutations. However, clinicians, patients and families may not be aware that gene-targeted therapies are available for a given individually-rare disorder. In addition, therapies are generally believed to be most effective in the early stages of a disorder or in the pre-symptomatic period before irreversible consequences of the disease have manifested, and the timing of therapeutics delivery is often critical to therapeutic success. To ensure that gene-targeted therapies move beyond the research environment and into the public health environment, NIH invited interested parties throughout the scientific research, advocacy, clinical practice, industry, and lay communities, including the public, to attend the three-day Gene-Therapies: Early Diagnosis and Equitable Delivery meeting, which was led by NCATS in June 2021, to discuss issues relating to the effective, efficient, and equitable distribution of gene-targeted therapies. The results of these discussions are being disseminated.[1637]

Microbiome

It has become increasingly clear that the healthy human body is filled with microorganisms, many of which play essential roles in health and disease. The human microbiome—as this ecosystem of microbes that live on and within people has been named—consists of a large but still undetermined number of microbes. Although bacteria represent the majority of the microbes that call our bodies home, other residents include single-celled archaea and fungi. Several types of viruses also live in the nose and gut of otherwise perfectly healthy people. Interactions between hosts and beneficial (“commensal") microbes have been demonstrated to play a key role in a range of important bodily functions, including regulation of metabolic processes and immune function, as well as reproduction and wound healing. Conversely, evidence indicates that dysregulated (“dysbiotic”) microbial communities can contribute to a wide range of diseases and conditions, including obesity, diabetes, cancer, and autoimmune diseases.

Summary of NIH Activities

Many NIH ICOs fund research on the microbiome, including NIA, NIAID, NIDDK, NIAMS, NIEHS, NEI, NLM, NIGMS, NCI, NHGRI, NCATS, NCCIH, ORWH, ODS, and the NIH Common Fund. NIH funding for microbiome

[1635] Anzalone AV et al. Nature 2019;576(7785):149-157. PMID: 31634902.
[1636] https://pave-gt.ncats.nih.gov/
[1637] https://ncats.nih.gov/rare-diseases/gene-targeted-therapies-events

research was $766 million in FY 2019, $852 million in FY 2020, and $864 million in FY 2021.[1638] Studies range from those aiming to develop tools for studying the microbiome to those using available tools to understand how the microbiome affects health and disease.

Understanding the Diversity of Microbes that Live On and Within Us

The diversity of the human microbiome is almost unimaginable. There may be more genes in the collective human microbiome (all the microbial genes from all the people on Earth) than stars in the observable universe—and at least half of these genes appear to be unique to the individual. A team of NIEHS supported microbiologists and bioinformaticians offer a first glimpse into the array of genes that make up this vast bacterial universe residing in each of us. The research is believed to be the largest analysis of its kind to date, and the first one to include DNA samples from bacteria that reside both in the mouth and the gut.[1639,1640] These data were also used to build a publicly available catalog of microbiome genes that other scientists can use to further advance the field. This is a first step in what will likely be a long journey toward understanding how differences in gene content drive microbial behavior and modify disease risk, and it will potentially inform the design of precision-targeted treatments.

The Human Microbiome Project, supported by the NIH Common Fund from 2007 to 2016, developed research resources that have enabled the study of the microbial communities that live in and on our bodies and the roles they play in human health and disease. Results from three long-term studies following host and microbiome characteristics (during pregnancy and preterm birth, inflammatory bowel disease, and prediabetes) were published in 2019. This research has expanded our understanding of the interaction between humans and our microbes and the resulting consequences for our health.[1641,1642] Key findings, datasets, and new techniques developed over the course of this second phase are expected to be used in hundreds of subsequent studies by other researchers to further advanced human microbiome research.

Understanding How the Microbiome Contributes to Health and Disease

The billions of organisms living on body surfaces, such as the skin of mammals (collectively referred to as microbiota) communicate with the host immune system and with each other in a sophisticated network. NIAID supported scientists and their collaborators have identified in mammals an internal communication network between skin cells, a common skin bacterium, and viruses integrated in the host genome (remnants of previous infections called endogenous retroviruses).[1643,1644] This novel communication network regulates tissue repair but also, in some settings, inflammation. This finding may potentially

---

[1638] https://report.nih.gov/funding/categorical-spending#/

[1639] Tierney BT, et al. *Cell Host Microbe* 2019 Aug 14;26(2):283-295.e8. PMID: 31415755.

[1640] https://hms.harvard.edu/news/microbial-fingerprinting

[1641] https://www.nih.gov/news-events/news-releases/human-microbiome-project-expands-toolbox-studying-host-microbiome-interactions

[1642] Integrative HMP (iHMP) Research Network Consortium. *Nature* 2019 May;569(7758):641-648. PMID: 31142853.

[1643] https://www.niaid.nih.gov/news-events/nih-scientists-describe-multi-kingdom-dialogue-between-internal-external-microbiota

[1644] Lima-Junior DS, et al. *Cell* 2021 Jul 8;184(14):3794-3811.e19. PMID: 34166614.

inform new treatments by providing insights on how tissue immunity is regulated by the microbiome and how diseases such as obesity and inflammatory skin disorders develop.

Histamine is a signaling molecule commonly associated with the symptoms of allergies, such as a runny nose, sneezing, and itching. Histamines also play an important role in immune response and neurotransmission. Previous research has focused mostly on endogenous histamine production, meaning histamine produced by the body's cells. NLM researchers used advanced computational methods to better understand the contributions of histamine produced by the human gut microbiota. They conducted a systematic search across 36,554 bacterial genomes for clues as to which microbes might be able to produce histamine. They then analyzed the relative abundance of these histamine-secreting microbes in the gut microbiome of colorectal cancer and inflammatory bowel disease patients. Histamine-secreting bacteria were present in much higher numbers in patients with inflammatory bowel disease compared with colorectal cancer patients, suggesting a possible association between histamine-secreting bacteria and inflammatory bowel disease.[1645] This work provides a comprehensive understanding of histamine-secreting bacteria in the human gut and identifies new potentially therapeutic targets for inflammatory and immunological diseases.

The study of the gut microbiome and its effects on health is an evolving scientific field, but current findings suggest connections to many health conditions, including obesity, metabolic disorders, inflammation, cancer, and depression. Recently, an NIA-supported research team analyzed gut microbiome genetic sequences and a wealth of other health and survival outcomes data from more than 9,000 people between the ages of 18 and 101. The investigators found that older adults who had a more unique pattern of changes to their gastrointestinal microbe profile tended to be healthier and live longer than peers with less microbiome divergence. The healthier participants' blood tests showed lower levels of LDL cholesterol and higher levels of vitamin D, but also more beneficial blood metabolites produced by gut microbes. In addition, people whose gut microbiomes had grown more unique with age were able to walk faster and had better overall mobility than peers who showed less gastrointestinal microbe changes with age. Plus, those with less diverse gut environments used more medications and were nearly twice as likely to die during the study period.[1646,1647] Further research is needed on the factors that influence the makeup of the gut microbiome, particularly the role of diet and physical activity.

The ocular microbiome, the sparse population of microorganisms that live on the surface of the eye, is believed to play a role in maintaining a healthy state, helping to regulate the immune response as the surface of the eye is exposed to bacteria from the environment. Imbalances within the ocular microbiome can trigger an inflammatory response and increase the risk for a number of eye diseases, including dry eye disease and Sjögren's syndrome, an immune system disorder characterized by dry eyes and dry mouth. To better understand the gaps and opportunities in the area, NEI hosted experts in a workshop entitled, "Investigating the Ocular Surface Microbiome: Best Practices for Low-Biomass Microbial

[1645] Mou Z, et al. *BMC Genomics* 2021 Sep 26;22(1):695. PMID: 34563136.
[1646] https://www.nia.nih.gov/news/unique-gut-microbiome-patterns-linked-healthy-aging-increased-longevity
[1647] Wilmanski T, et al. *Nat Metab* 2021 Feb;3(2):274-286. PMID: 33619379.

Research."[1648] This workshop facilitated discussion about technical issues including collecting specimens and generating reproducible data. Following this workshop, NEI released a solicitation for research proposals[1649] that aim to improve our understanding of ocular pain and dry eye disease, and to spur new discoveries and move the field forward.

Understanding How the Microbiome Can Inform New Treatments, Therapies, and Clinical Guidelines

Scientists know that the microbiome can protect people from bacterial infections, but little is known about the molecular pathways or how they provide protection. NIH-funded scientists are studying the gut microbiome with a goal of finding or enhancing natural treatments that can replace antibiotics. This class of drugs is commonly used to fight bacterial infections, but can both harm beneficial bacteria and become less effective over time at killing harmful bacteria as those bacteria develop drug resistance. Scientists from NIAID and four other ICs, studying the body's natural defenses against bacterial infection, have identified a nutrient, taurine, that helps the gut recall prior infections and kill invading bacteria. Taurine given to mice as a supplement in drinking water successfully prepared their gut microbiota to prevent future infection.[1650,1651] This finding could aid efforts seeking alternatives to antibiotics.

Recent studies suggest that major changes occur in the gut microbiota during pregnancy. These studies could help explain why pregnant women with lupus, an autoimmune disease where the body's immune system attacks its own tissues and organs, have a higher risk of worsening symptoms after delivery. New findings from NIAMS supported researchers studying lupus-prone pregnant, postpartum, and control mice, found that beneficial and pathogenic gut bacteria might be targeted therapeutically to change their compositions for beneficial effect.[1652] While further studies in humans are warranted, diet and probiotics would be relatively easy and tolerable approaches for modulating gut microbiota and potentially improving disease management for lupus patients, especially those planning on having children.

Rheumatoid arthritis (RA) is an autoimmune disease resulting in inflammation and painful swelling in the affected areas of the body, usually the joints (knee, shoulder, elbow, hands, etc.) Oral methotrexate (MTX) is a first-line therapy for RA, but it is inadequate in about 50 percent of patients.[1653] A NIAMS-supported multidisciplinary study discovered that MTX also has off-target effects on the growth, gene expression, and metabolic activity of diverse gut bacteria that are broader than previously appreciated. These off-target effects carry potential downstream consequences. In mice, MTX changes the composition of their gut microbiome and reduces their ability to mount a full immune response.[1654] These results provide insight into the mechanisms by which the microbiome affects the treatment of rheumatologic disease. Defining these mechanisms will advance knowledge on the role of the microbiome in precision medicine

[1648] https://www.nei.nih.gov/about/news-and-events/events/investigating-ocular-surface-microbiome-best-practices-low-biomass-microbial-research
[1649] https://grants.nih.gov/grants/guide/rfa-files/RFA-EY-22-001.html
[1650] https://www.niaid.nih.gov/news-events/nih-scientists-identify-nutrient-helps-prevent-bacterial-infection
[1651] Stacy A, et al. *Cell* 2021 Feb 4;184(3):615-627.e17. PMID: 33453153.
[1652] Mu Q, et al. *Microbiome* 2019 Jul 16;7(1):105. PMID: 31311609.
[1653] Aletaha D, et al. *An Observ Study J Rheumatol.* 2002;29:1631–8. PMID: 12180721.
[1654] Nayak RR, et al. *Cell Host Microbe* 2021 Mar 10;29(3):362-377.e11. PMID: 33440172.

and help develop predictive tools to guide therapy and identify druggable microbial targets, which would personalize the care of rheumatology patients.

It is now widely accepted that the microbiome plays an essential role in numerous biological processes, diseases, and conditions, from obesity and diabetes to autoimmune diseases such as RA. NIAMS-supported scientists may have just added cartilage regeneration to this growing list. Researchers investigating whether the gut microbiome in the Murphy Roths large (MRL/MpJ) strain of laboratory mice—informally termed "super-healer mice" due to their improved ability to heal injuries—was associated with ear cartilage regeneration identified several groups of related microbes that, when present, correlated with improved ear cartilage healing. Intriguingly, they also found evidence that suggests some of the ear cartilage regenerative ability of MRL/MpJ mice can be transferred to normal mice through a gut microbiome transplantation.[1655] This results in an intriguing possibility that the gut microbiome may contribute to cartilage inflammation and regeneration and could affect the development of osteoarthritis. The regeneration-associated microbiome groups identified in this research have also been reported in other osteoarthritis-relevant studies, which opens the possibility of using gut microbiome manipulation as an osteoarthritis treatment.

Hidradenitis suppurativa (HS) is a chronic, debilitating, and inflammatory skin disease that causes skin bumps that can be painful. While there is no cure, sometimes antibiotics taken by mouth can be helpful, suggesting that bacteria may be an important component of this disease. In a recent study, NIAMS-funded researchers characterized the skin microbial community using genomic sequencing and other state of the art technologies to identify differences in the bacteria on the skin of patients with HS compared with healthy volunteers. They also compared those with mild and more severe HS disease.[1656] They found increased bacterial diversity in HS subjects as compared with healthy volunteers. These findings lay the groundwork for future studies investigating how bacterial changes on the skin may play a role in HS and in other diseases.

Atopic dermatitis (AD), the most common form of eczema, is a chronic condition that makes the skin red, itchy, and uncomfortable. A bacteria called *Staphylococcus aureus* (SA) often makes the disease worse by colonizing the affected area and promoting inflammation. Treatments are limited to avoiding irritants like soap and using creams or ointments to provide some relief from itching. In a phase 1 clinical trial, NIAMS supported researchers tested the safety and mechanisms of action of using a beneficial bacterium isolated from healthy human skin, called *Staphylococcus hominis A9* (ShA9), as a topical therapy for AD.[1657] The researchers determined that ShA9 cleared some strains of SA and inhibited a toxin it produces, although it did not significantly decrease AD severity.[1658] However, the finding that ShA9 is safe opens a new avenue of topical therapeutics that may change the clinical skin research field in the near future.

[1655] Velasco C, et al. *PLoS One* 2021 Jul 20;16(7):e0248322. PMID: 34283837.
[1656] Naik HB, et al. *J Invest Dermatol* 2020 Apr;140(4):922-925.e3. PMID: 31539533.
[1657] https://clinicaltrials.gov/ct2/show/NCT03151148
[1658] Nakatsuji T, et al. *Nat Med* 2021 Apr;27(4):700-709. PMID: 33619370.

Granulomatosis with polyangiitis (GPA) is a type of vasculitis characterized by inflammation of the blood vessels that disrupts blood flow and oxygen supply, thereby damaging tissues and organs.[1659] Taking advantage of an unbiased gene sequencing approach, NIAMS-supported investigators documented significant and dynamic changes in the nasal bacterial community over time in GPA patients. The study generated additional support for the role of the *Staphylococcus* bacterial family in GPA, but also unexpectedly implicated the *Corynebacterium* bacterial family, a lesser-known and poorly studied family of nasal bacteria, as a potential instigator of the disease.[1660] Future studies are needed to better understand the mechanisms underlying host–microbial interactions in GPA. These will pave the way to identifying potential therapeutic targets for early treatment and help develop new measures for prediction of disease relapse.

Researchers recently discovered that the gut microbiome may play an important role in helping malnourished children. Recent findings from an ongoing series of studies (supported by NIDDK, NIAMS, NIGMS, NCATS, and NCI) of malnourished children living in Bangladesh demonstrated that complementary foods (i.e., foods given in addition to those consumed in the diet) that boost maturation of the gut microbiome can improve markers of normal growth, neural development, and immune function in these children. The benefits of this microbiome-directed approach outweighed those of the standard supplementary foods used to treated childhood malnutrition.[1661,1662] Through further developing and testing complementary foods that are custom-designed to reverse microbiome immaturity caused by malnutrition, scientists hope to provide the means to more fully restore health to these children.

Minority Health and Health Disparities

NIH devotes special priority to minority health and health disparities to ensure that the healthcare needs of all populations are considered. Health disparities research focuses on the health differences that adversely affect disadvantaged populations. This includes targeting research efforts towards women, racial and ethnic minority populations, sexual and gender minority populations, people with lower socioeconomic status, as well as populations that live in underserved rural areas. In the U.S., recent Census data show that racial and ethnic diversity is increasing. Currently, about 18.7 percent of the total U.S. population is Hispanic or Latino, followed closely by Black or African American at 12.1 percent.[1663] In addition, in 2010, about 19.3 percent of the U.S. population lives in rural areas where access to healthcare and other social services is a key issue.[1664]

Minority health research—the scientific investigation of distinctive health characteristics and attributes of racial and/or ethnic minority groups who are usually underrepresented in biomedical research—is a priority for NIH and is critically important for the health of our nation. NIH continues to devote

[1659] https://www.mayoclinic.org/diseases-conditions/granulomatosis-with-polyangiitis/symptoms-causes/syc-20351088
[1660] Rhee RL, et al. *Arthritis Rheumatol* 2021 Sep;73(9):1703-1712. PMID: 33682371.
[1661] Gehrig JL, et al. *Science* 2019 Jul 12;365(6449):eaau4732. PMID: 31296738.
[1662] Chen RY, et al. *N Engl J Med* 2021 Apr 22;384(16):1517-1528. PMID: 33826814.
[1663] https://www.census.gov/library/stories/2021/08/2020-united-states-population-more-racially-ethnically-diverse-than-2010.html
[1664] https://www2.census.gov/census_2010/04-Summary_File_1/

considerable resources to health disparities research. Minority health research aims to provide a better understanding of why certain populations have poorer health outcomes, to provide greater scientific knowledge about the influence of health determinants, and to translate this knowledge into interventions to address differences in health outcomes. Research findings have consistently shown that health disparities can arise from biological differences, as well as exposure to and behaviors developed within societal, cultural, and environmental contexts. The result is gradients in health mediated by such factors as physiology, behavior, and gene expression. As a result of these efforts, a complex web of interconnected and overlapping factors influencing health has been identified and informs how health is addressed not only among racial and ethnic minority populations, but among all Americans.

Summary of NIH Activities

In keeping with its role as the nation's primary steward of biomedical and behavioral research, NIH is committed to improving minority health and eliminating health disparities in the U.S. at the individual, community, regional, and national levels. NIH-designated U.S. populations that experience health disparities include Black or African American, Hispanic or Latino, Asian American, AI/AN, Native Hawaiian and Other Pacific Islander populations, socioeconomically disadvantaged populations, underserved rural populations, and sexual and gender minority populations. NIMHD is charged with coordinating and leading the NIH vision and programs on minority health and health disparities research, envisioning an America in which all populations have an equal opportunity to live long, healthy, and productive lives.[1665] In addition, research on minority health and health disparities is conducted and funded throughout the NIH, including THRO and SGMRO. Established in 2015, THRO was established in recognition of the importance of ensuring meaningful input from and collaboration with Tribal Nations on NIH programs and policies, and coordinates activities related to Tribal health research and scientific priorities for AI/AN.[1666] Also established in 2015, SGMRO coordinates sexual and gender minority (SGM) population-relevant research and activities by working directly with NIH ICOs.[1667] ORWH is dedicated to promoting research on the health of women.[1668] NIH funding for Health Disparities was $3,381 million in FY 2019, $3,484 million in FY 2020, and $4,362 million in FY 2021.[1669] NIH funding for Minority Health was $3,188 million in FY 2019, $3,314 million in FY 2020 and $3,729 million in FY 2021.[1670] NIH funding for Rural Health was

[1665] https://www.nimhd.nih.gov/about/overview/mission-vision.html
[1666] https://dpcpsi.nih.gov/thro
[1667] https://dpcpsi.nih.gov/sgmro
[1668] https://orwh.od.nih.gov/
[1669] https://report.nih.gov/funding/categorical-spending#/. Reporting for this category does not follow the standard RCDC process. This category uses a different approach consisting of a manual review of projects qualified by NIH subject matter experts applying the category's definition. These categories also permit pro-ration based on percentage enrollment in the studies of minority subjects as defined by the Office of Management and Budget or of otherwise disadvantaged persons such as, but not inclusive of, less privileged socio-economic status populations, underserved rural residents, and sexual and gender minorities. Additionally, training investigators of minority or disadvantaged backgrounds, research performed at minority serving institutions, and outreach and communication are included in these categories.
[1670] https://report.nih.gov/funding/categorical-spending#/. Reporting for this category does not follow the standard RCDC process. This category uses a different approach consisting of a manual review of projects qualified by NIH subject matter experts applying the category's definition. These categories also permit pro-ration based on percentage enrollment in the studies of minority subjects as defined by the Office of Management and Budget or

$541 million in FY 2019, $728 million in FY 2020, and $774 million in FY 2021. NIH funding for SGM/LGBTQ* was $258 million in FY 2019, $276 million in FY 2020, and $341 million in FY 2021.[1671] NIH funding for American Indian or Alaska Native was $214 million in FY 2019, $308 million in FY 2020 and $305 million in FY 2021.

Below are examples of efforts to address minority health and health disparities across the following main categories:

- Theory, Measures, and Methods Related to Minority Health
- Training Programs to Advance Minority Health and Health Disparities Research
- COVID-19 Related Studies to Advance Minority Health and Identify and Address Health Disparities
- Community Driven Research and Partnering with Other Federal Agencies
- Upstream Causes of Health Disparities
- Prevention
- Rural Populations
- Women's Health, Including Maternal Health
- Sexual and Gender Minority Populations
- Underserved Racial and Ethnic Populations
- Chronic Diseases

Theory, Methods, and Measures Related to Minority Health and Health Disparities

NIH-funded efforts have been conceptualizing and developing appropriate theoretical frameworks as well as approaches for measurement and methodologies to better understand and address minority health and health disparities. This includes constructing frameworks for researchers to examine minority health

of otherwise disadvantaged persons such as, but not inclusive of, less privileged socio-economic status populations, underserved rural residents, and sexual and gender minorities. Additionally, training investigators of minority or disadvantaged backgrounds, research performed at minority serving institutions, and outreach and communication are included in these categories.

[1671] https://report.nih.gov/funding/categorical-spending#/. This category includes projects that are focused on basic, pre-clinical, clinical, biomedical, health services, behavioral, and social research relevant to SGM populations. The SGM population - often referred to as LGBT, is asterisked to recognize the diversity in membership as well as sensitivities associated with the variety of descriptive names in use by the medical communities and general public. LGBT research pertains to people whose sexual orientation is not exclusively heterosexual, i.e. lesbian, gay, and bisexual persons. Research projects can likewise focus on individuals whose gender identity differs from the sex originally assigned to them at birth (such as transgender, gender non-confirming, gender fluid or bi-gender), or who may not self-identify as LGBT (such as queer, questioning, two-spirit, asexual, etc.). Research also can cover individuals who are born with conditions in which development of chromosomal, gonadal, or anatomic sex is atypical, i.e. people who identify themselves as intersex or with differences/disorders of sex development (DSD). DSD can include, but are not limited to: Y chromosome aneuploidy, congenital adrenal hyperplasia, complete androgen insensitivity, partial androgen insensitivity, gonadal dysgenesis, mixed gonadal dysgenesis, hypospadias, Klinefelter syndrome, Turner syndrome, 5aRD2 deficiency, aromatase defects, MRKH syndrome and gynecomastia. For further information please refer to the SGMRO website: https://dpcpsi.nih.gov/sgmro

and health disparities and identifying ways to conceptualize and measure these factors. Below are highlights of some of the key activities in this area.

NIMHD developed the Minority Health and Health Disparities Research Framework (see Figure 40) as a guide for scientists conducting health disparities research.[1672] The framework is a model that depicts a wide array of health determinants relevant to understanding and addressing minority health and health disparities and promoting health equity. The framework identifies multiple domains and levels of influence that may contribute to health disparities throughout life. Since its establishment, the NIMHD Research Framework has been adapted to guide research for populations experiencing health disparities including AI/AN, Native Hawaiian, Puerto Rican, and sexual and gender minority populations, and to address vaccine hesitancy in the southern U.S.

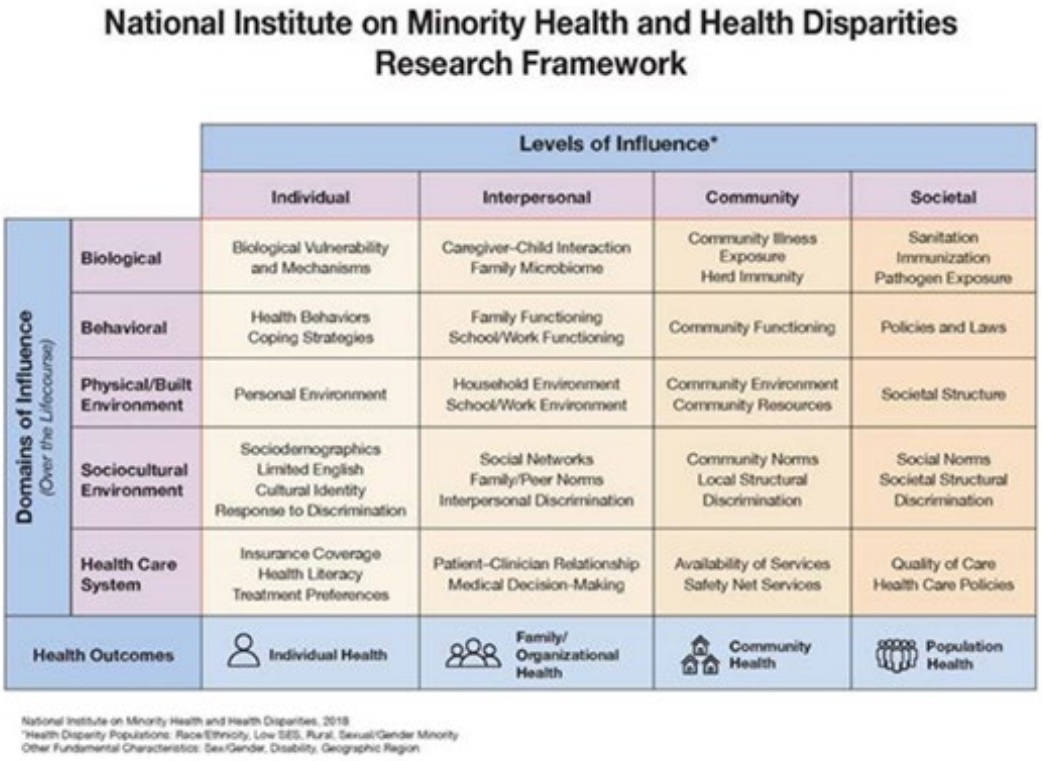


Figure 40: National Institute on Minority Health and Health Disparities Research Framework

NIMHD staff, along with leading experts from around the country, authored *The Science of Health Disparities*, a 26-chapter textbook to cover the spectrum of health disparities research.[1673] The textbook is designed to help researchers better understand the framework for conducting minority health and health disparities science. *The Science of Health Disparities Research* provides state-of-the-science

[1672] https://www.nimhd.nih.gov/about/overview/research-framework/nimhd-framework.html
[1673] Dankwa-Mullan I, et al. *The Science of Health Disparities Research* 2021. ISBN: 978-1-119-37485-5.

information on advancing theory, refining measurement, improving investigative methods, and diversifying scientific research, and:

- Defines the field of health disparities science
- Explains basic definitions, principles, and concepts for identifying, understanding, and addressing health disparities
- Suggests new directions in scholarship and research
- Discusses population health training, capacity building, and the transdisciplinary tools needed to advance health equity

NIMHD and leading experts also published additional resources about structural racism, discrimination, and the macro-level conditions such as residential segregation and institutional policies that limit opportunities, resources, power, and the well-being of individuals and populations based on race or ethnicity and less privileged status. Racism and discrimination are increasingly recognized as social determinants of health that contribute to poorer health outcomes over the life course for racial and ethnic minorities and other populations who experience health disparities. These resources highlight the need for a broader approach to reduce health disparities that addresses the interconnected systems perpetuating racism and other forms of discrimination. The authors provide recommendations for increasing focus on structural racism and discrimination, outline a framework for considering the experiences of different racial and ethnic groups, and identify future research directions including research examining the ways that racism is embedded in online systems contributes to health disparities.[1674]

Following the 2018 NIH SGMRO-hosted workshop on research opportunities in SGM-related methods and measurement, several ICs have collaborated to solicit projects that explore Methods and Measurement in Research with SGM Populations. Research projects funded under this initiative conduct methods and measurement research relevant to SGM populations. SGM populations include, but are not limited to, individuals who identify as lesbian, gay, bisexual, asexual, transgender, two-spirit, queer, and/or intersex. Individuals with same-sex or -gender attractions or behaviors and those with a difference in sex development are also included. These populations also encompass those who do not self-identify with one of these terms but whose sexual orientation, gender identity or expression, or reproductive development is characterized by non-binary constructs of sexual orientation, gender, and/or sex.[1675]

In addition, NIMHD led the development and released the PhenX Social Determinants of Health Assessments Collection to provide standard measurement protocols for researchers to use in studying social determinants of health related to health disparities. This compendium of standard measures is available in the Phenotypes and eXposures Toolkit (PhenX Toolkit) and facilitates research by providing

[1674] Williams DR, et al. Ethn Dis. 2021 May 20;31(Suppl 1) PMIDs: 34045828, 34045829, 34045830, 34045831, 34045832, 34045833, 34045834, 34045835, 34045836, 34045837, 34045838, 34045839.
[1675] https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-20-005.html

access to a collection of measures vetted by an expert panel to assess individual and structural social determinants of health.[1676]

Living in a disadvantaged neighborhood is linked to a variety of negative health outcomes, including higher rates of diabetes and cardiovascular disease, increased usage of health services, and early death. Without accounting for neighborhood disadvantages, health interventions and policies may be ineffective. The Neighborhood Atlas, funded by NIA, shares data regarding disadvantaged neighborhoods with the public to make metrics available for use in research, program planning, and policy development.[1677]

Training Programs to Advance Minority Health and Health Disparities

NIH invests in training researchers to explore issues related to minority health and health disparities. For example, NIA supports and participates in a variety of initiatives aimed at recruiting and retaining researchers from diverse backgrounds, including those from traditionally underrepresented population groups, at all education and career levels into aging research. Each summer, NIA offers the intensive Butler-Williams Program for junior faculty and researchers new to the field of aging to gain insight about aging research.[1678] In addition, NIA supports dissertation research grants to support diversity in aging research, as well as predoctoral, postdoctoral, and career transition awards specifically to promote diversity in translational research for Alzheimer's Disease and Related Dementias (AD/ADRD).[1679]

Another training mechanism funded by NIA is the Resource Centers for Minority Aging Research (RCMAR), which are designed to enhance the diversity of the aging research workforce by mentoring promising scientists from diverse backgrounds, including those from underrepresented groups, for sustained careers in aging research in priority areas of social, behavioral, and economic research on aging, and to develop infrastructure to promote advances in these areas while simultaneously increasing the number of researchers focused on health disparities and the health and well-being of racial and ethnic minority older adults.[1680] The program supports research at multiple levels from genetics to cross-national comparative research, and at stages from basic through translational, with the goal to improve the health, well-being, function, and independence of older Americans. In 2018, support for the RCMAR program was expanded to support eight additional centers focused on priority areas of social and behavioral science related to AD.

NIMHD led efforts to publish an *American Journal of Public Health* supplement documenting the NIMHD science visioning process to transform minority health and health disparities research, culminating in 30 key strategies for researchers to employ to advance the science of minority health and health disparities research. These strategies include developing methods and measurements for health disparities, research on etiology that examine racism, the life course, biology, health services and social determinants, as well as structural, behavioral, and multi-level interventions to reduce health disparities. The supplement

[1676] https://www.nimhd.nih.gov/programs/collab/phenx/
[1677] https://www.neighborhoodatlas.medicine.wisc.edu/
[1678] https://www.nia.nih.gov/research/osp/butler-williams-scholars-program
[1679] https://www.nia.nih.gov/research/training/training-opportunities-special-populations
[1680] https://rcmar.org/

presents research and perspectives focused on expanding methodological approaches to monitor and reduce health disparities for racial and ethnic minority populations.[1681]

COVID-19 Related Studies to Advance Minority Health and Identify and Address Health Disparities

In FY 2020, NIH invested $500 million to launch the Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) program, aimed at understanding effective strategies and interventions to increase reach, access, and uptake of SARS-CoV-2 testing among underserved and vulnerable groups.[1682] RADx-UP is a consortium of community-engaged projects across the U.S. linked by a Coordinating and Data Collection Center. Researchers partner with churches, non-profit organizations, school districts, community health centers, and other community-based organizations to evaluate interventions to increase access and uptake of testing for communities disproportionately impacted by the COVID-19 pandemic, as well as to better understand and alleviate barriers to SARS-CoV-2 testing.

NIH released several funding opportunities to support the RADx-UP program which was launched in two phases:

Phase 1:

- Emergency Competitive Revisions for Community-Engaged Research on COVID-19 Testing among Underserved and/or Vulnerable Populations, which supports two-year community-engaged testing research projects to examine SARS-CoV-2 infection patterns and efforts to increase access and effectiveness of diagnostic methods through supplements to individual NIH research awards.[1683]
- The Limited Competition for Emergency Competitive Revisions for Community-Engaged Research on COVID-19 Testing among Underserved and/or Vulnerable Populations, funds large-scale networks, consortia, Centers, and other current programs that have adequate capacity, infrastructure, and established community-engaged relationships to conduct large-scale testing.[1684]
- Emergency Competitive Revisions for Social, Ethical, and Behavioral Implications Research on COVID-19 Testing supports research to identify, analyze, and address the social, ethical, and behavioral factors likely to influence access and uptake of SARS-CoV-2 testing in underserved and/or vulnerable populations.[1685]
- Emergency Awards: RADx-UP Coordination and Data Collection Center (CDCC) a national resource to provide overarching support and guidance in coordinating across RADX-UP projects in

[1681] Borrell LN., Vaughan R. *Am J Public Health*. 2019 Jan;109(S1): S6-S7. PMID: 30699024.
[1682] https://www.nih.gov/research-training/medical-research-initiatives/radx/funding, https://radx-up.org/
[1683] https://grants.nih.gov/grants/guide/notice-files/not-od-20-120.html
[1684] https://grants.nih.gov/grants/guide/notice-files/not-od-20-121.html
[1685] https://grants.nih.gov/grants/guide/notice-files/not-od-20-119.html

Administrative Operations and Logistics, SARS-CoV-2 Testing Technology, Community and Health System Engagement, and Data Collection, Integration and Sharing.[1686,1687]

The RADx-UP program launched Phase 2 by funding projects at ten institutions across eight states to build evidence on returning students, teachers, and support staff to in-person school safely, in school districts with diverse students in underserved geographic locations. The RADx-UP CDCC also launched the Community Collaboration Mini-Grant and Rapid Research Pilot Program and funded the first group of awardees.[1688]

As a result of these and other investments made by NIH, several studies have revealed important insights related to COVID-19 and health disparities. For example, a study funded by NIMHD estimated the prevalence of COVID-19-related discrimination among major U.S. racial and ethnic groups and the associations between discrimination, race and ethnicity, and other sociodemographic characteristics, using data from the nationally representative COVID-19's Unequal Racial and Ethnic Burden. [1689] Overall, 22.1 percent of participants reported experiencing discriminatory behaviors and 42.7 percent of participants reported people around them acting afraid because they think the participant might have COVID-19. All racial and ethnic minority populations were more likely to experience COVID-related discrimination, with Asian and AI/AN adults being most likely. Limited English proficiency, lower education, lower income, and residing in a big city or the Southeast Central U.S. also increased discrimination prevalence. This study highlighted the need for efforts to minimize and discredit racially driven language and discrimination around COVID-19 and future epidemics.

Another study supported by NIA used nationally representative data to model disparities around COVID-19 to show that adults with 12 or fewer years of education, those in the bottom quartile of household income, and non-Hispanic Blacks are more likely to have three or more risk factors for COVID-19 (e.g., hypertension, diabetes, cancer) than those with a college degree, those in the top income quartile, and non-Hispanic Whites, respectively. Notably, those with 12 or fewer years of education were more than twice as likely to have three or more COVID-19 risk factors relative to those with a college degree, while those in the bottom income quartile were four times more likely to have three of more risk factors relative to those in the top quartile. Across the socioeconomic categories of education, income, and race-ethnicity, older age predicted greater COVID-19 risk, thereby compounding potential risk for older and more disadvantaged individuals.[1690]

Other NIA-supported research identified disproportionate reductions in projected life expectancy due to COVID-19 among U.S. African American or Black and Hispanic or Latino individuals relative to White individuals. Researchers estimated life expectancy in the U.S., both in the scenario of the COVID-19 pandemic and in the scenario of the pandemic having not occurred, to provide a measure of the pandemic's impact on life expectancy. Life expectancy projections were also stratified by race and

[1686] https://grants.nih.gov/grants/guide/rfa-files/rfa-od-20-013.html
[1687] https://reporter.nih.gov/search/KXAba1mqnUiPpckO5HTEDw/project-details/10233289
[1688] https://radx-up.org/
[1689] Strassle PD, et al. *Am J Public Health.* 2022 Mar;112(3):453-466. PMID: 35196054.
[1690] Wiemers EE, et. al. *Res Soc Stratif Mobil.* 2020 Oct; 69:100553. PMID: 32921870.

ethnicity. The resulting models indicated that the pandemic reduced U.S. life expectancy by 1.13 years to 77.48 years, which reflects the lowest average lifespan since 2003. Relative to the 0.68-year reduction in life expectancy for White, African American or Black individuals experienced reduction in life expectancy of 2.10 years, which is more than three times greater than the reduction in life expectancy among White individuals, and Hispanic or Latino individuals experienced reductions in life expectancy of 3.05 years, which is more than four times greater than the reduction in life expectancy among White individuals.[1691]

Community Driven Research and Partnering with Other Federal Agencies

Advancing health equity for communities is a complex challenge that extends beyond the reach of traditional health care settings. Therefore, innovative, community-driven research is needed to develop a health equity research agenda focused on multisector structural interventions addressing critical social determinants of health. NIH funds research to address the multiple community level factors that contribute to health inequities. For example, the NIH Common Fund's Community Partnerships to Advance Science for Society (ComPASS) aims to catalyze, develop, and evaluate community-driven, health equity structural interventions that leverage multisectoral partnerships to advance health equity and facilitate and implement a framework across many ICs for health equity structural intervention research. The ComPASS program began planning in 2021, including a series of community listening sessions, and received conceptual approval by the NIH leadership in January 2022.[1692]

Another example of this effort is the Research Gaps and Opportunities Workgroup of the NIDA Racial Equity Initiative (REI).[1693] In February 2021, the workgroup convened a virtual meeting to discuss research gaps in racial inequities in substance use and addiction. More than 1,300 attendees registered for the event. Through keynote presentations and discussion panels, researchers who concentrate on the social determinants of health and their influence on SUDs and scientists knowledgeable of the effects of racial discrimination on biology relevant to addiction provided feedback that will inform NIDA's efforts to promote racial equity. Specifically, the workgroup offered recommendations for NIDA's REI Action Plan regarding synergies in health disparities and addiction research, research opportunities for SDOH and basic science, and best practices and ways to measure progress.

NLM's Information Resource Grants to Reduce Health Disparities support projects that bring useful and understandable health information to populations affected by health disparities, and their health care providers. A total of ten new awards were made during FY 2019-2021. Grants awarded in FY 2021 aim to reduce health disparities by increasing access to and dissemination of information resources on heart and blood vessel disease for Puerto Ricans, developing an accessible informed consent app-based toolkit for people who are deaf and hard of hearing and want to participate in research, and developing a digital resource that provides provide traditional indigenous health knowledge along with widely available

[1691] Andrasfay & Goldman. *Proc Natl Acad Sci USA.* 2021 Feb 2;118(5): e2014746118. PMID: 33446511.
[1692] https://dpcpsi.nih.gov/sites/default/files/2.10PM-CF-Concept-COMPASS-onepager-Zenk-Gordon-FINAL-508.pdf
[1693] https://nida.nih.gov/news-events/meetings-events/2021/02/enhancing-health-disparities-research-related-to-substance-use-addiction-research-gaps-opportunities

evidence- based and emergent practices for diabetes and cardiovascular disease prevention for urban AI/AN and Indigenous community members and health care providers.[1694,1695,1696]

NIH also partners with other agencies to develop practical ways to share information regarding minority health disparities. For example, the NIH partners with the Indian Health Service (IHS) and the Administration for Community Living (ACL) to distribute an electronic newsletter entitled *Honoring Health: Resources for American Indians and Alaska Natives*.[1697] The newsletter's purpose is to increase awareness of health information and resources from NIH and other Federal agencies. It is distributed to AI/AN intermediaries, specifically IHS Community Health Workers and ACL Title VI grantees working with Native elders. Each issue features a relevant health topic and highlights resources, events, training, and grants and funding opportunities.

Upstream Causes of Health Disparities

Research shows that health disparities are tied to upstream causes such as racism, housing instability, food insecurity, interpersonal violence, childhood trauma, and other factors.[1698] A recent study, supported in part by NINR, examined the relationships among multiple social determinants of health factors (income, education, and discrimination), cardiovascular health (body mass index and smoking), and depressive symptoms among young African American or Black mothers.[1699] The study found that in young socioeconomically disadvantaged African American or Black mothers, elevated body mass index and perceived discrimination were significantly associated with higher reported depressive symptoms, an example of the impact of social determinants on health outcomes.

NIH has also devoted considerable effort towards identifying the effects of specific types of upstream causes of health disparities, such as food insecurity and inadequate nutrition. Nutrition plays an important role throughout our lives in promoting health and preventing disease. Where people live or how much money people earn can affect the ability to access or afford healthy food choices. Ensuring food security and access to healthy food are key to preventing disparities in a variety of diet-related diseases and conditions, such as cardiovascular disease, obesity, diabetes, and cancer. Elucidating the role of these social conditions on diet and nutritional status could help address and prevent diet-related health disparities and promote health equity. ONR held a virtual workshop in 2021 to review the state of the science, identify research gaps and opportunities related to food insecurity and the neighborhood food

[1694] https://reporter.nih.gov/search/QV48nu0ZQUqJYk2b6hQjZw/project-details/10291646
[1695] https://reporter.nih.gov/search/QV48nu0ZQUqJYk2b6hQjZw/project-details/10291517
[1696] https://reporter.nih.gov/search/QV48nu0ZQUqJYk2b6hQjZw/project-details/10291203
[1697] https://dpcpsi.nih.gov/thro/news-events/honoring-health
[1698] National Academies of Sciences, Engineering, and Medicine 2019. *Integrating Social Care into the Delivery of Health Care: Moving Upstream to Improve the Nation's Health.* Washington, DC: The National Academies Press. https://doi.org/10.17226/25467
[1699] Millender E, et al. *Arch Psychiatr Nurs.* 2021 Feb;35(1):94-101. PMID: 33593522.

environment, and suggest innovative research strategies that will inform policy and practice to address and prevent diet-related health disparities and promote health equity.[1700]

Figure 41: Food Insecurity, Neighborhood Food Environment, and Nutrition Health Disparities: State of the Science Workshop. Credit: NIH

Moreover, health disparities are an intergenerational problem in the U.S. Although these begin to form early in life within one generation, health disparities propagate into the next generation through multiple life course pathways, causing socioeconomically disadvantaged groups and members of racial and ethnic minority populations to face disproportionate burdens of morbidity and shortened life expectancy. To address these disparities, NIH funds novel research ideas that focus on identifying upstream causes of health, prevalence of specific types of upstream causes of health disparities, and interventions to address upstream causes of health disparities and advance health equity. A recent NIH-funded study analyzed the prevalence and contributing factors of food insecurity among Pediatric Intensive Care Unit (PICU) families at a major urban medical center.[1701] Of the 137 families in the study, 20 percent were food insecure, and 21 percent participated in Supplemental Nutrition Assistance Program. African American or Black families reported a higher prevalence of food insecurity compared with White families (56 percent vs 30 percent). Prevalence of food insecurity among PICU families was double the general U.S. population. As a result of these findings, expanded universal social determinants of health screening and support in the PICU have been implemented.

Many NIIH-funded initiatives adopt multiple approaches to advance knowledge of the social determinants of human development in diverse populations. Based on the Developmental Origins of Health and Disease and Life-Course Epidemiological approaches, the Rhode Island Children's Health Equity and Development

[1700] https://www.nhlbi.nih.gov/events/2021/food-insecurity-neighborhood-food-environment-and-nutrition-health-disparities; https://www.labroots.com/ms/virtual-event/food-insecurity-neighborhood-food-environment-nutrition-health-disparities-science

[1701] La Count S, et al. *Pediatr Crit Care Med.* 2021 Apr 1;22(4): e275-e277. PMID: 33790215.

Study aims to investigate prenatal and early life mechanisms for socioeconomic and racial and ethnic disparities in child health and development and investigate life course pathways underlying health disparities during adolescence and adulthood.[1702]

Prevention

The HHS Healthy People 2030 initiative provides a strategic framework for a national prevention agenda that communicates a vision for improving health and achieving health equity.[1703] It identifies science-based, measurable objectives with targets to be achieved by the end of the decade. The overarching goals of Healthy People focus on attaining healthy, thriving lives and well-being, eliminating health disparities, creating social, physical, and economic environments that promote health and well-being, promoting healthy development and behaviors, and engaging leadership and constituents to take action and design policies. ODP provides input and guidance on Healthy People activities and coordinates Healthy People activities across NIH ICOs. ODP staff serve on the Federal Interagency Workgroup, the principal advisory body for the development of the Healthy People initiative. ODP, through its co-funding program, has provided financial support and subject matter expertise for the development of new Healthy People 2030 Foundation Health Measures, Data Collection for Assessing the Well-Being of the Nation, new data visualization and health disparities measurement, and dissemination and implementation of evidence-based resources. In 2019-2021, ODP staff convened meetings for all NIH participants in Healthy People workgroups and participated in several planning meetings for the launch of Healthy People 2030.

NIH is investing funds into developing new preventive interventions and strategies to address health issues faced by underserved populations and overcome health disparities. The Advancing Prevention Research for Health Equity (ADVANCE) initiative is an NIH-wide effort to develop funding opportunity announcements on new preventive interventions and strategies to deliver existing evidence-based interventions and preventive services in populations that experience health disparities, focusing on leading risk factors for death and disability. ADVANCE will develop funding announcements through four NIH-wide workgroups centered around clusters of leading risk factors/preventive services: cardiometabolic risk factors, alcohol, tobacco, and other drugs, mental health, and cancer screening and preventive services.[1704]

NIH launched the Disparities Elimination through Coordinated Interventions to Prevent and Control Heart Disease Risk program and awarded the first projects to seven grantees in different areas of the country to work with local communities to evaluate a variety of proven interventions for conditions such as asthma, cardiovascular disease (CVD), and hypertension. In Louisiana, community health workers will partner with local churches to reduce CVD risk in African American or Black individuals by promoting lifestyle interventions in line with current CVD guidelines (e.g., healthy diet, physical activity, smoking cessation, weight loss). In rural Colorado, researchers will work with school-based asthma navigators and nurses to test a team approach to asthma control in school children. In Los Angeles, 51 adult primary care clinics

[1702] https://www.nichd.nih.gov/about/org/dir/dph/officebranch/sbsb/social-determinants
[1703] http://healthypeople.gov
[1704] https://prevention.nih.gov/research-priorities/health-disparities#ADVANCE

will implement culturally-tailored multi-level evidence-based strategies to improve blood pressure control.[1705]

NIH also awarded eleven grants to support the work of exceptionally creative researchers across the U.S. through the NIH Common Fund's Transformative Research to Address Health Disparities and Advance Health Equity initiative. The awards investigated such issues as financial interventions that address structural racism, telehealth-driven technologies in community-based interventions for mental health, cancer health equity among diverse deaf, deafblind, and hard-of-hearing populations, and health disparities in underserved rural and socioeconomically disadvantaged children.[1706]

Disparities in health care delivery and health outcomes present distressing challenges to underserved populations, who often experience a greater burden of chronic diseases and are more likely to show signs of poor disease management. Health information technology (IT) tools may serve a vital role in reducing such disparities in the clinical care setting. NIMHD published a supplement in the June 2019 issue of *Medical Care*, "Addressing Health Disparities Through the Utilization of Health Information Technology."[1707] The authors discuss the potential application of health IT in reducing disparities by increasing access to care, improving quality of healthcare and by promoting better patient-clinician communication.

NIEHS-funded researchers along with parents and children co-designed SunSmart, a digital intervention against sun exposure targeted at Hispanic and underserved populations, who are likely to underestimate their risk for skin cancer.[1708]

The Los Angeles Barbershop Blood Pressure Study, funded by the NCATS CTSA program and NHLBI, has continued to improve upon its innovative model of hypertension care for non-Hispanic African American or Black men that links health promotion by barbers to medication management by pharmacists. After promising initial results, where 64 percent of the participants were able to reduce their blood pressure to healthy levels and keep it under control for a year, a follow-on study was done to see if telemedicine visits could provide the same benefits with higher efficiencies and lower costs. Telemedicine has been widely adopted since the start of the COVID-19 pandemic, and this study showed that conducting pharmacist follow-up barbershop visits virtually can help address barriers to care and reduce costs and inefficiencies, while maintaining patient health outcomes.[1709]

Rural Populations

According to the latest Census Bureau statistics, about 20 percent of the U.S. population lives in rural areas.[1710] Rural Americans face unique challenges as access to health care, social services, and other

[1705] https://decipheralliance.org/
[1706] https://commonfund.nih.gov/healthdisparitiestransformation, https://www.nih.gov/news-events/news-releases/new-highly-innovative-nih-research-awards-address-health-disparities-advance-health-equity
[1707] https://www.nimhd.nih.gov/about/publications/hit2019.html
[1708] Huh J, et al. *Int J Behav Med.* 2021 Dec;28(6):768-778. PMID: 33846955.
[1709] Blyler CA, et al. *J Am Heart Assoc.* 2021 Jul 6;10(13): e020796. PMID: 34155907.
[1710] https://mtgis-portal.geo.census.gov/arcgis/apps/MapSeries/index.html?appid=49cd4bc9c8eb444ab51218c1d5001ef6

necessary community resources are limited. To better understand the unique challenges faced by rural Americans and the best way to address their health needs, NINR released a funding announcement to encourage research to promote a better understanding of the challenges faced by rural population groups, for the development (or adoption/adaptation) of evidence-based interventions that can reduce health risks faced by rural Americans. Both prevention and treatment interventions are needed to address rural health issues. Prevention strategies should address and measure reductions in risk factors and enhancement of protective factors, while treatment approaches would seek to measure and address amelioration of health in individuals living with existing conditions. To accomplish these goals, the research community is encouraged to use a wide range of culturally appropriate methodological approaches that can enhance access to and acceptability of interventions in rural settings, such as telehealth and community-based prevention research, where appropriate. It is the expectation that research supported under this solicitation will contribute to our knowledge of the sustainability of health promotion and disease prevention strategies in rural settings.[1711]

Another NIH-supported study, the Risk Underlying Rural Areas Longitudinal Cohort Study,[1712] investigates what causes the high rates of chronic obstructive pulmonary disease and other chronic diseases in Southeastern rural communities. The study uses a mobile clinic equipped with the latest diagnostic technologies to collect health data from about 4,000 residents aged 35-64 in ten rural counties in Alabama, Kentucky, Louisiana, and Mississippi. The study also collects socioeconomic and environmental data and is expected to inform disease prevention strategies for rural Americans.

An NIMHD-funded study examined the relationship of psychosocial factors, such as self-efficacy, family role modeling, and perceptions of the environment on diet, physical activity, and sedentary behavior in Hispanic or Latino children living in rural Washington State. Gender, height, and weight were obtained from children eight to twelve years old from two rural communities in Lower Yakima, Washington. Psychosocial measures, diet, and screen time were obtained for a subsample of 179 children. Higher fruit and vegetable self-efficacy scores were associated with more consumption of fruits and vegetables, more engagement in physical activity, and less time spent sedentary per day. Male gender and some psychosocial measures were associated with obesogenic behaviors. Findings suggest enhanced understanding of the factors associated with obesity-related behaviors in rural, Hispanic or Latino children may inform the development of effective behavioral health interventions for this population.[1713]

Breast cancer survivors are at risk of neuroimmune dysfunction in survivorship due to chronic emotional and psychosocial stressors following breast cancer treatment. An NIMHD-funded research project studied relationships between neuroimmune activity and perceived health in rural and urban breast cancer survivors. The study found differences in immune activity between rural and urban breast cancer survivors but found no observable differences between the rural and urban group in neuroendocrine activity. Results suggests that rural-urban residence may be a factor in relationships between neuroimmune function and perceived health status, particularly social functioning in women with breast

[1711] https://grants.nih.gov/grants/guide/rfa-files/RFA-NR-20-001.html
[1712] https://www.theruralstudy.org/
[1713] Rillamas-Sun E, et al. *J Racial Ethn Health Disparities*. 2019 Dec;6(6):1218-1227. PMID: 31385261.

cancer.[1714] Residents in IDeA states, especially those living in rural areas, often have less access to health care and therefore tend to suffer from poorer health outcomes. Several IDeA states have the highest maternal and infant mortality rates. To address this critical issue, NIGMS and ORWH, in conjunction with several other NIH ICs, are providing administrative supplements to IDeA grants to increase research directed toward women's health and health disparities with a special interest in maternal and infant morbidity and mortality. NIGMS seeks to expand the capacity of IDeA states to conduct research that addresses women's health.[1715,1716]

Women's and Maternal Health

Women's health is of critical importance as women often face unique health care challenges and disparities. NIH is targeting efforts broadly towards women's health issues as well as maternal health. Below are several studies undertaken to better understand the unique challenges faced by women, and to advance women and maternal health. For additional information, please see the section on Women's Health and Pregnancy Outcomes of this Chapter.

Hysterectomy, or removal of the uterus, is a frequent surgical procedure with major consequences for women's health and well-being. An NIH-funded study examined health disparities by racial and ethnic identity in hysterectomy rates. Specifically, researchers analyzed data on all inpatient and outpatient hysterectomy procedures performed in North Carolina from 2011 to 2014. Estimates that accounted for the portion of the population who had previously undergone the procedure showed that non-Hispanic African American or Black women and non-Hispanic American Indian women had higher hysterectomy rates than non-Hispanic White women. Hysterectomy rates for Hispanic or Latina, and non-Hispanic Asian and Pacific Islander women were lower than the rates for non-Hispanic White women. Further research is necessary to better understand the underlying causes of these differences to ensure that women of all races and ethnicities are provided with appropriate care.[1717]

Lupus is a chronic autoimmune disease that affects females more than males, with African American or Black individuals developing more severe manifestation of the disease. Since patients with lupus, especially among African American or Black individuals, display an accelerated disease course relative to the general population, the traditional blood biomarkers of elevated low-density lipoproteins and total cholesterol levels do not accurately assess their heart disease risk. A newly discovered blood biomarker may provide a better way to diagnose and treat African American or Black patients with lupus than standard CVD screening procedures, the efficiency of which has been called into question because lipid profiles differ between individuals of African American or Black and those of European ancestry.[1718]

[1714] Hulett et al., *Cancer Nurs.* 2021 Jul-Aug;44(4):323-332. PMID: 32195710.
[1715] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-20-017.html
[1716] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-21-018.html
[1717] Gartner DR, et al. *Epidemiology.* 2020 May;31(3):385-392. PMID: 32251065.
[1718] Hammad SM, et al. *Front Immunol.* 2021 Jul 21;12:694318. PMID: 34367153.

Maternal health efforts aim to ensure optimal health of women before pregnancy, during pregnancy, childbirth, and after pregnancy. One of HHS' missions is to reduce maternal mortality and improve health outcomes for pregnant women.[1719]

NIH-funded research suggests racial and ethnic disparities exist in maternal health outcomes and maternal mortality. An NICHD-funded study reexamined information on death certificates from 2016 and 2017. Researchers found that the maternal mortality rate among non-Hispanic African American or Black women was 3.5 times higher than among non-Hispanic White women—a larger disparity than had been previously reported and that these disparities were concentrated among a few causes of death. For example, postpartum cardiomyopathy (disease of the heart muscle) and the blood pressure disorders preeclampsia and eclampsia were leading causes of maternal death for African American or Black women. Pregnant and postpartum African American or Black women were two to three times more likely than White women to die of hemorrhage (severe bleeding) or embolisms (blood vessel blockages).[1720] Another analysis of nationally representative data on inpatient care of 207,730 women who were readmitted to the hospital postpartum found serious disparities in the risk of severe morbidity and a range of life-threatening complications. Overall, non-Hispanic African American or Black women were significantly more likely than all other groups of women to be readmitted. Compared with non-Hispanic White women, these women were particularly at risk for cardiopulmonary complications, with a risk of pulmonary edema (fluid in the lungs) and/or acute heart failure more than twice as high as that of non-Hispanic White women. Other complications experienced more frequently included sepsis, shock, hysterectomy, and transfusion.[1721]

An NICHD-supported study evaluated hospitals in New York City, ranking performance for its treatment and outcomes for pregnant women and very preterm newborns.[1722] The findings of the study found that African American or Black and Hispanic or Latina women, when compared to White women, were less likely to deliver in "excellent" hospitals and more likely to deliver in "poor" quality hospitals. Importantly, their findings were not explained by differences in insurance coverage, maternal education, or other sociodemographic and clinical factors. The researchers emphasized that maternal and neonatal disparities because of hospital quality can lead to poor health outcomes that affect lifelong health and wellness.

The relationship between racial discrimination and preterm labor, a key measure of maternal health, is an understudied area in research. An NIMHD-funded study examined the associations between preterm labor and direct and vicarious racial discrimination among African American or Black women at three life stages: childhood, adolescence, and adulthood. Findings showed a 48 percent increase in the odds of preterm labor with each unit increase in adolescent direct racial discrimination. Each unit increase in childhood vicarious racial discrimination was associated with a 45 percent increase in the odds of preterm labor. The results reveal an association between life-stage racial discrimination and preterm labor risk among African American or Black women, which underscores the need for further research to understand

[1719] https://www.hhs.gov/sites/default/files/call-to-action-maternal-health.pdf
[1720] MacDorman MF, et.al. *Am J Public Health.* 2021 Sep;111(9):1673-1681 PMID: 34383557.
[1721] Aziz A. et al., *Am J Obstet Gynecol*. 2019 May;220(5): 484.e1-484.e10. PMID: 30786255.
[1722] Howell EA, et al. *Matern Child Health J.* 2020 Jun;24(6):687-693. PMID: 32303940.

how direct and vicarious racial discrimination at different developmental periods impact racial disparities in birth outcomes.[1723]

In addition to race and ethnicity, geography plays a role in health disparities. NICHD-supported researchers evaluated maternity care deserts—counties that lack hospitals with obstetric care and obstetrician or certified nurse midwife providers—in Louisiana. The findings from this study showed that the risk of death during pregnancy and up to 1 year after delivery was significantly higher for women who lived in these healthcare "deserts." In addition, they found major racial inequalities in these risks that went beyond geographical access to maternal healthcare.[1724] Another NICHD-funded study reported that pregnant women in rural areas across the U.S. were more likely to have a blood transfusion during labor and delivery, compared to woman in more urban areas.[1725] Studies such as these aim to identify tangible ways to improve health outcomes for women who live in rural and underserved areas.

Sexual Gender and Minority Populations

Sexual and gender minority populations refer to individuals who identify as lesbian, gay, bisexual, asexual, transgender, two-spirit, queer, and/or intersex. NIH supported research has uncovered important insights to improve health for these populations. Small-scale studies and observations suggest that transgender people are at a heightened risk for criminal victimization. Recently, an analysis using the National Crime Victimization Survey, a national primary source of nonfatal criminal victimization statistics, provided further evidence that transgender people experienced violence at a higher rate compared with cisgender people.[1726] Between transgender and cisgender women, there was a large and statistically significant difference in the percentage of violent victimizations believed to be hate motivated. Rates of victimization did not differ between transgender women and men.

NIH also conducts research on the impact of treating transgender/gender-diverse (TGD) individuals with hormones. TGD youth are treated early in their pubertal development with gonadotropin-releasing hormone agonists (GnRHas) to stop innate puberty and to prevent the development of secondary sex characteristics. One large multisite study of TGD youth in the U.S. looked at the differences in rates at which an adolescent experiences the fastest growth in their stature in the first year of receiving GnRHa treatment. They found that overall, TGD youth who received the GnRHa treatment early in their pubertal development had growth rates similar to that of prepubertal children. However, when GnRH therapy was initiated at later pubertal development, TGD youth experienced less growth in stature compared to the prepubertal range of age matched peers.[1727]

Racial Health Disparities

Racial disparities in health and health care outcomes are well documented and NIH continues to invest in this important area. NIH-funded researchers found that African American women, who typically are assumed to have lower risk of osteoporosis than White women, had less knowledge of osteoporosis than

[1723] Daniels KP. et al. *Matern Child Health J.* 2020 Nov;24(11):1387-1395. PMID: 32920761.
[1724] Wallace M, et al. *Womens Health Issues.* 2021 Mar-Apr;31(2):122-129. PMID: 33069560.
[1725] Hartenbach EM, et al. *Obstet Gynecol.* 2020 Mar;135(3):685-695. PMID: 32028506.
[1726] Flores AR, et al. *Am J Public Health.* 2021 Apr;111(4):726-729. PMID: 33600251.
[1727] Schulmeister C, et al. *J Adolesc Health.* 2022 Jan;70(1):108-113. PMID: 34315674.

their white counterparts. The women felt their health was controlled more externally whereas White women felt their health was internally controlled by their own behavior. African American or Black women need a strong, trusting relationship with their health-care providers; this was not observed in White women. The African American or Black women deemed osteoporosis a lower priority when having to consider multiple health conditions, and they were less likely to address an osteoporosis diagnosis through steps including taking medication.[1728]

Another study aimed to evaluate the association of race with post-operative care or hospital readmissions after total knee arthroplasty (TKA). NIAMS-funded researchers analyzed data from 107,768 patients who underwent TKA from April 2012 to September 2015.[1729] Black patients were 2.5- to 5-fold more likely than White patients to be discharged to an inpatient rehabilitation facility or skilled nursing facility rather than home health care or home self-care.

NIH has invested research on racial health disparities related to specific diseases. Below are some key studies that have been funded by NIH.

NIDA research, funded through the HEAL Initiative, found that disparities in opioid overdose deaths continue to worsen for Black people. Non-Hispanic Black individuals in four U.S. states experienced a 38 percent increase in the rate of opioid overdose deaths from 2018 to 2019, while the rates for other race and ethnicity groups held steady or decreased.[1730]

Tobacco smoke exposure (TSE) is a hazard for children. NIEHS funded research used data from the National Health and Nutrition Examination Survey for 1999-2014 to investigate how the prevalence of TSE defined by level of cotinine varied among U.S. children (3-11 years old), and to calculate differences between sociodemographic characteristics and TSE by two-year increases. They found that TSE prevalence declined from 64.5 percent to 38.1 percent during 1999-2014, and that there was a decline among all socio-demographic groups. In 2013-2014, differences in TSE were found by race and ethnicity, family monthly poverty level, and housing status. African American or Black children were 1.85 times more likely to be exposed to tobacco smoke than White children, whereas Hispanic Mexican children were at lower risk of exposure. The study showed that exposure to smoke increased with higher levels of family poverty. Children who lived in rented homes were 2.23 times more likely to be exposed than children who lived in owned homes. Targeted tobacco control efforts are needed to reduce existing TSE disparities among children, especially those who are African American or Black, of low socioeconomic status, and who live in rented homes.[1731]

To determine whether cumulative blood pressure (BP) levels can explain racial differences in cognitive decline, NINDS-funded researchers pooled individual participant data from five cohorts from January 1971 to December 2017. The primary outcome was change in global cognition, and secondary outcomes were change in memory and executive function. Higher BP levels in African America or Black individuals were

[1728] Wright NC, et al. *J Racial Ethn Health Disparities.* 2019 Aug;6(4):707-718. PMID: 30747331.
[1729] Singh JA, et al. *JAMA Netw Open*. 2019 Oct 2;2(10): e1914259. PMID: 31664446.
[1730] Larochelle MR, et al. *Am J Public Health*. 2021 Oct;111(10):1851-1854. PMID: 34499540.
[1731] Merianos AL. et al. *Prev Med*. 2019 Jun; 123:138-142. PMID: 30902698.

associated with faster decline, compared with White individuals, in global cognition and memory but not executive function. This important longitudinal study demonstrates health disparities that are linked to racial differences in later-life cognitive decline.[1732]

An NINR-funded study explored the association between return to work and mental health outcomes in African American or Black men living and recovering from serious traumatic injuries in Philadelphia. The study found that men who did not return to work after a serious traumatic injury had almost three times the odds of poor mental health when compared to men who did return to work. The study also found that younger age, lack of insurance or public insurance, and higher lifetime experience of racism were independently associated with both return to work and screening positive for depression or post-traumatic stress disorder. Programs to optimize recovery after injury in African American or Black men should include consideration of key structural factors such as employment, financial stability, and the impact of racism-related exposures.[1733]

The nation is facing a critical and growing need for people living with Alzheimer's and related dementias to participate in clinical trials. That need is especially acute for frequently underrepresented groups in research, such as African American or Black and Hispanic Americans, who also facing a higher burden of AD/ADRD. NIA supports several initiatives aimed at expanding recruitment to clinical research — particularly recruitment of members of underserved groups to clinical trials of interventions to prevent or treat AD/ADRD. These include:

- A National Recruitment Strategy, developed with broad community input, enumerating goals and strategies for enhancing recruitment to support research, including clinical trials. The strategy outlines practical, proactive approaches to help study sites engage a wider, more diverse number of volunteers.[1734]
- An AD/ADRD Clinical Studies Recruitment Planning Guide, available on the NIA website, to support study coordinators and other recruitment team members in recruiting diverse populations to AD/ADRD clinical trials. The guide includes information and tips about how to plan and implement community partnerships, promote health and science literacy, and address bias in workforce diversity.[1735]
- The NIA's Alzheimer's Disease Outreach, Recruitment, and Engagement Resources (ADORE) repository offers resources to support the recruitment and retention of participants into clinical trials and studies on AD/ADRD. ADORE includes materials and activities developed by NIA-supported Alzheimer's Disease Research Centers (ADRCs) and other grantees. The database also includes relevant resources from other organizations, as well as published research articles.[1736] Please see Chapter 4 for more information on ADRCs.

[1732] Levine DA, et al. *AMA Neurol*. 2020 Jul 1;77(7):810-819. PMID: 32282019.
[1733] Palumbo AJ, et.al. *Injury.* 2021 Apr;52(4):750-756. PMID: 33627251.
[1734] https://www.nia.nih.gov/research/recruitment-strategy
[1735] https://www.nia.nih.gov/sites/default/files/2019-05/ADEAR-recruitment-guide-508.pdf
[1736] https://www.nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources#:~:text=Home%20Research%20%26%20Funding,Alzheimer's%20%26%20Dementia%20Outreach%2C%20Recruitment%20%26%20Engagement%20Resources,keyword%2C%20or%20explore%20by%20tags

- OutreachPro is a new online research tool to help increase participation by traditionally underrepresented populations in AD/ADRD clinical trials. This tool enables researchers and communities to create and customize clinical trial recruitment communications such as websites, handouts, videos, and social media posts. OutreachPro offers templates that can be tailored using a central library of messages, headlines, photos, and text that have been extensively tested among individuals representing diverse and underserved populations.[1737]
- The Clinical Research Operations and Management System (CROMS) is a new system that will provide critical and real-time information to ensure that NIA-supported clinical studies are making significant progress toward the inclusion of recruitment goals related to multiple underrepresented groups, including African American or Black, Hispanic, and Asian American populations. While the initial emphasis will be on collecting enrollment data for AD/ADRD studies, eventually, CROMS will be expanded to include clinical research in all topic areas.[1738]
- The Alzheimers.gov Clinical Trials Finder is a database of more than 250 clinical trials and studies that are actively recruiting for AD/ADRD research. The Clinical Trials Finder is searchable by location and provides a general description and contact information for each trial or study.[1739]

Chronic Diseases

NIMHD released a funding opportunity announcement and made 11 awards to support regional comprehensive research centers on the prevention, treatment, and management of chronic diseases associated with health disparities.[1740] The Centers will conduct research on chronic diseases that disproportionately affect populations with health disparities, including, but not limited to, obesity, diabetes, hypertension, coronary heart disease, congestive heart failure, asthma, chronic kidney disease, chronic liver disease, stroke, osteoarthritis, and certain cancers. Please see Chapter 4 for more information on the NIMHD centers of excellence.

To support these centers, NIMHD released a funding announcement for the Research Coordinating Center to Reduce Disparities in Multiple Chronic Diseases (RCC RD-MCD).[1741] This center coordinates activities across the chronic disease centers including data collection, promoting collaboration and communication among researchers and the broader research community, promoting skills development of early-stage researchers, coordinating and managing in-person and/or virtual meetings, and facilitating community engagement efforts.

NIMHD released a funding announcement to develop Comprehensive Care for Adults with Type 2 Diabetes Mellitus from Populations with Health Disparities.[1742] This initiative supports innovative research to develop, test and evaluate multi-level/multi-component strategies (including models of health care) to

[1737] https://outreachpro.nia.nih.gov/
[1738] https://www.nia.nih.gov/research/grants-funding/nias-clinical-research-operations-management-system-croms
[1739] https://www.alzheimers.gov/clinical-trials
[1740] https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-21-007.html
[1741] https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-21-008.html
[1742] https://grants.nih.gov/grants/guide/pa-files/pa-21-232.html

effectively adapt and implement comprehensive clinical care for individuals with Type 2 diabetes mellitus from populations with health disparities concordant with recommended and evidence-based guidelines.

NIMHD, with support from NIEHS and NICHD, launched an effort to establish Specialized Centers of Excellence on Environmental Health Disparities Research.[1743] These Centers of Excellence support multidisciplinary research, research capacity building, and community-engaged research activities focused on understanding and reducing or eliminating environmental health disparities, defined as inequities in population health mediated by disproportionate adverse exposures associated with the physical, chemical, social, and built environments.

Women's Health and Pregnancy Outcomes

Women face unique health problems, and even those health conditions that strike men and women in nearly equal numbers can often have unique consequences or complications for women. Researchers are discovering the critical roles that sex (being male or female) and gender identity (including social and cultural factors) play in health, wellness, and disease progression. The discoveries made through the study of women's health and sex differences are key to advancements in personalized medicine for both sexes.[1744]

Women's health focuses on the many health issues and conditions that are female-specific or that affect women differently than men, and it includes many aspects of women's health, from cancer to cardiovascular diseases, to autoimmune diseases, to menstrual irregularities, to infertility. It also includes phases of life and health from birth, to pregnancy, to menopause and beyond. A subfield of women's health called "maternal health" focuses on pregnancy.

Summary of NIH Activities

Women's health research is an essential part of the NIH research agenda. The goal is to improve the lives of women everywhere. The field has expanded far beyond its roots in reproductive health and includes the study of health throughout the lifespan and across the spectrum of scientific investigations, from basic research and laboratory studies to molecular research, genetics, and clinical trials. Researchers are investigating healthy lifestyles and behavior, risk reduction, and disease prevention, and searching for the best ways to diagnose and treat chronic conditions.

Women's health and maternal health are a central part of NICHD's mission, although this research is carried out across NIH ICOs. In recognition of the importance of advancing research in this field, NIH established the Office of Research on Women's Health (ORWH) in the NIH OD. In 1993, Congress passed the *NIH Revitalization Act*, which, among other things, established ORWH in statute. ORWH, which celebrated its 30th anniversary in 2020, stimulates and encourages basic, translational, and clinical research on the role of sex and gender in health and disease, and sets NIH research priorities in those diseases, disorders, and conditions that primarily affect women.[1745]

[1743] https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-20-001.html
[1744] https://orwh.od.nih.gov/research/funded-research-and-programs/what-womens-health-research
[1745] https://orwh.od.nih.gov/

In FY 2019, 2020, and 2021, respectively, NIH funded $4,469 million, $4,466 million, and $4,610 million in research on Women's Health; [1746] $487 million, $550 million, and $537 million in research on Pregnancy; $334 million, $407 million, and $422 million in research on Maternal Health. Maternal Morbidity and Mortality was added as a new RCDC category in 2020, where NIH funding levels were $224 million and $240 million in FY 2020 and 2021 respectively.

This section includes updates on some of NIH's activities during FY 2019–2021 relating to women's health and maternal health. Additional updates, as they pertain to specific health areas, are included in other sections of this chapter, as appropriate, such as the Life Stages, Human Development, and Rehabilitation section.

Women's Health

The area of women's health focuses on the many health issues and conditions that are female-specific or that affect women differently than men. Guiding research on this topic across NIH, the *2019–2023 Trans-NIH Women's Health Strategic Plan* prioritizes broad aspects of women's health research to be addressed over the next five years.[1747] To assist NIH ICOs with incorporating women's health implementation and evaluation plans into their individual strategic plans, ORWH recently led efforts across NIH to develop a guide to facilitate these processes.[1748]

In December 2021, ORWH published the *NIH Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health (Women's Health Biennial Report) for FYs 2019–2020.*[1749] The report describes the NIH-wide programs and accomplishments that fulfill ORWH's core mission. The biennial report also provides highlights from research, supported by NIH ICOs, on women's health and on the influence of sex and gender on health and disease. In addition, the report presented NIH women's health research spending for FY 2019, including data from FY 2017–2018 for comparison purposes. The report also documents the inclusion of women and racial and ethnic minorities in NIH-funded clinical research during these years. The *NIH Sex as a Biological Variable*[1750] and *Inclusion*[1751] policies help to ensure that women, and female biology in general, are factored into every stage of research. The *FYs 2019–2020 NIH Report on the*

[1746] https://report.nih.gov/funding/categorical-spending#/. Reporting for this category now more closely follows the standard RCDC process compared with the project identification, cost pro-ration, and validation procedures used for FY 2018 and prior fiscal years. Individual Institutes, Centers, and Offices (ICOs) previously classified reportable awards using subjectively-defined criteria and assigned funding based on percentages of female subjects included in the studies. In FY 2019, subject matter experts across ICOs achieved consensus that the allocation of women's health-related spending should be grounded on scientific relevance and developed new prorating guidance, accordingly. To ensure a robust reporting transition, starting FY 2019, ICOs applied the new definitions only to the competing projects and retained the previous prorating schemes for the non-competing awards and will gradually roll-out from the inclusion-based approach in the subsequent fiscal years. In conjunction with the described efforts, NIH also instituted the use of an automated Manual Categorization System (MCS) to enhance workflow efficiency and standardize the NIH-wide cost allocation practices.

[1747] https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Strategic_Plan_2019_508C_0.pdf

[1748] Noursi S et al. Glob Adv Health Med 2021;24(10). PMID: 34458015.

[1749] https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_BiennialReport2019_20_508.pdf

[1750] https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable

[1751] https://orwh.od.nih.gov/womens-health-research/clinical-research-trials/nih-inclusion-policies

Advisory Committee on Research on Women's Health presented data on awardees' plans to conduct analysis by sex/gender in NIH-defined phase 3 clinical trials. This addressed the final of five recommendations included in a 2015 Government Accountability Office (GAO) report, which NIH has been implementing over the past few years.[1752] New to the report is a section entitled *NIH Workforce and Grantees.*[1753] This section provides information that seeks to aid and inform discussions on areas of improvement and parity within NIH and the broader scientific communities. This section includes information on roles, programs, and occupations of women in the NIH workforce for FY 2019–2020, and information on NIH grant funding by sex and/or gender, race, and ethnicity for FY 2016–2020. An entry on *NIH Report of the Advisory Committee on Research on Women's Health* is included in Appendix B of this report.

In FY 2019, ORWH issued an FOA entitled *The Intersection of Sex and Gender Influences on Health and Disease* to stimulate research that incorporates and enhances our understanding of the influence and intersection of sex and gender in health outcomes across a broad array of scientific disciplines.[1754] It is the only NIH-wide funding opportunity that focuses broadly on the health of women, and researchers were encouraged to consider health disparities populations and life course. The initiative was expanded in FY 2020 to include investigations that address cutting-edge studies on the SARS-CoV-2 virus or COVID-19 to better understand sex and gender differences pertaining to COVID-19, including a focus on therapeutics and vaccines, access to care, the outcome of patient interactions with health care providers, and mortality due to co-morbid conditions.[1755] Despite the fact that this was a new and unique funding opportunity, there was robust response and the success rate for applications submitted by institutions supporting new and early-stage investigators represent almost half of the awardees for this program, which speaks to the competitiveness of these new investigators and the burgeoning interest in research at the intersection of sex and gender.

In response to a request by Congress in October 2021, NIH convened a conference, *Advancing NIH Research on the Health of Women*, to evaluate research currently underway related to women's health, specifically regarding the following three topics: maternal morbidity and mortality, rising rates of chronic debilitating conditions in women, and stagnant cervical cancer survival. The opportunities identified as a result of the conference will be used to guide future ORWH activities related to women's health research.[1756]

[1752] In the GAO report entitled *Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research (GAO 16–13),* GAO examined enrollment of women and efforts to monitor such enrollment in NIH-funded clinical research and NIH's endeavors to ensure that NIH-funded clinical trials are designed and conducted to analyze potential sex differences, when applicable. GAO recommended that NIH examine and report more detailed data on women's enrollment in NIH-funded research and collect, analyze, and report data on the extent to which these studies include analyses of potential differences between men and women. The report is available at: https://www.gao.gov/products/GAO-16-13

[1753] https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_BiennialReport2019_20_508.pdf

[1754] https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-029.html

[1755] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-168.html

[1756] https://orwh.od.nih.gov/research/2021-womens-health-research-conference

Figure 42: ORWH sought broad input to identify research priorities and funding. Credit: NIH/OD/DPCPSI/ORWH

The COVID-19 pandemic underscores the need to systematically consider sex and social determinants of health, including gender, to strengthen our collective capacity to respond equitably to COVID-19 and any threats related to future outbreaks or pandemics. To complement the *NIH-Wide Strategic Plan for COVID-19 Research*,[1757] and to guide its COVID-19 response, ORWH developed *Guiding Principles: Sex and gender influences in COVID-19 and the health of women*.[1758] These guiding principles aid the research community in considering the range of biological and social factors relevant to COVID-19 and the health of women. Accounting for sex without considering gender (and other social determinants of health) would limit the development and deployment of effective, equitable diagnostics, treatments, and interventions relevant to the entire population. Incorporating a sex-and-gender lens, ORWH developed an annotated digest and bibliography to provide NIH staff, researchers, and the extramural community, with curated background content, research frames, and resources related to sex and social determinants of health to facilitate alignment of the NIH response with the 2019-2023 *Trans-NIH Strategic Plan for Women's Health Research.*[1759]

NIH works with different communities across the U.S. to promote women's health. NIEHS and ORWH support Women's Health Awareness Day,[1760] a free annual community event that supports the women of Durham, North Carolina, and surrounding counties. It provides health awareness education, information, and resources, as well as on-site health screenings. The goals of the event are to: inform women and empower them to take responsibility for their health; encourage women to understand their health options; and identify services, resources, and products that best help them prevent poor health. This helps reduce the number of health issues for participants and supports health equity.

[1757] https://covid19.nih.gov/nih-strategic-response-covid-19
[1758] https://orwh.od.nih.gov/sites/orwh/files/docs/ORWHGuidingPrinciple.pdf
[1759] https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Strategic_Plan_2019_508C_0.pdf
[1760] https://www.niehs.nih.gov/research/programs/wha/annual_conference/index.cfm

As previously mentioned, a broad range of research on women's health is supported across NIH ICOs, which acts to drive discovery forward on all fronts. For example, animal models have provided valuable insight into the mechanisms of underlying human disorders that affect women differently than men. A recent study, supported by NICHD and NINDS, suggests that early intervention could delay and reduce symptoms in Rett syndrome. Mutations in the X-linked gene *MECP2* cause Rett syndrome, a severe and progressive neurological disorder that affects primarily girls, which currently has no effective treatments. Children with Rett syndrome develop normally for their first one or two years of life and then develop profound motor and cognitive decline. In this study, a team of researchers hypothesized that intensive motor and cognitive training during the early period of normal development could reduce the severity of eventual disease. In a mouse model of Rett syndrome, they showed that beginning intensive training in the presymptomatic period, but not after symptom onset, improved performance on motor and memory tasks and significantly delayed the onset of disease symptoms. The researchers also showed that the improvements were associated with structural and functional changes in neurons that were repeatedly activated during training. These results suggest a rationale for genetic screening that would identify children affected by Rett syndrome early and allow for presymptomatic intervention. Similar strategies may also be applicable to other neurodevelopmental disorders.[1761]

An increasing number of young American women have one or more cardiovascular risk factors, such as obesity, sleep apnea, or high blood pressure. A recent analysis looking at blood pressure trajectories over decades found that in women, blood pressure elevation occurs earlier and progresses more rapidly throughout life, as compared to the same trajectory in men. This early-onset sexual difference may set the stage for later-life CVDs that tend to present differently—not simply later—in women compared with men.[1762] For these reasons, addressing maternal morbidity and mortality will require a life-course approach that focuses on improving women's heart health before, during, and after reproductive age.

Reproductive Health

Reproductive health refers to the condition of male and female reproductive systems during all life stages and is covered in the Urologic and Gynecologic Diseases and Conditions subsection of the Chronic Diseases and Organ Systems section of this chapter. Because reproductive health is an important component of NIH's women's health agenda, some of NIH's recent advances, as they pertain to women's health, will be covered here.

NIH is conducting research into various biological, behavioral, and environmental factors that influence reproductive health. In 2020, NIEHS launched a study to examine behavioral and environmental exposures and reproductive health, such as menstrual cycles, conception, pregnancy loss, and pregnancy outcomes. Researchers are using existing data (including self-reported data and assay results) from the 1982-1986 North Carolina Early Pregnancy Study and a subsequent 2010-2011 cohort follow-up study.[1763]

[1761] Achilly NP et al. Nature. 2021;592(7855):596-600. PMID: 33762729.
[1762] Ji H, et al. *JAMA Cardiol* 2020 Mar 1;5(3):19-26. PMID: 31940010.
[1763] https://clinicaltrials.gov/ct2/show/NCT04595760?term=National+Institute+of+Environmental+Health+Sciences&recrs=adf&draw=2

One environmental factor under investigation in another NIEHS-supported study is ambient temperature, which has been found to affect the ability to conceive. A diminished ovarian reserve (the number and quality of a woman's eggs) reduces a woman's ability to get pregnant. NIEHS-funded researchers found that women exposed to higher temperatures had a lower ovarian reserve. Exposure to higher temperatures was associated with a lower antral follicle count, a measure of ovarian reserve. Study findings raise concerns that the steady increase in global temperature due to climate change may result in accelerated reproductive aging in women.[1764,1765]

An NICHD- and NCATS-supported study found that hormonal intrauterine devices (IUDs) were as effective as a copper IUD for emergency contraception, and with less discomfort. Researchers completed a randomized clinical trial to compare the effectiveness of copper and hormone-releasing IUDs for emergency contraception. The hormone-releasing IUD contains levonorgestrel, a synthetic form of the reproductive hormone progesterone. Compared with the copper IUD, the levonorgestrel IUD has been shown to reduce heavy bleeding and menstrual discomfort. For emergency contraception, the levonorgestrel IUD appeared to be as effective as the copper IUD, and users reported less discomfort with its use. The study did not compare the emergency contraceptive effectiveness of IUDs to that of emergency contraceptive pills. However, the pregnancy rate of 0.3 percent in the study was lower than the 1.4 to 2.6 percent pregnancy rate reported by studies of emergency contraceptive pills.[1766]

NICHD's Contraceptive Clinical Trials Network (CCTN)[1767] supports clinical field centers that are selected for their capacity to conduct phase 1, 2, and 3 trials of oral, vaginal, intrauterine, injectable, implantable, or topical contraceptive drugs and devices. Contraceptive research and development is critical for providing safer, more effective methods of preventing unintended pregnancies. NICHD-supported researchers are exploring better contraceptive methods for women, particularly non-hormonal options that a woman can use on demand, as well as developing contraceptives that offer protection against STIs, offering women better control over their reproductive health and well-being.

Maternal Health

A maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.[1768] In 2021, 1,205 women died of maternal causes in the U.S.[1769] NIH is one of many federal agencies working to improve maternal health and pregnancy outcomes, with the goal of preventing and treating pregnancy-related complications to reduce maternal morbidity and mortality (MMM). Maternal morbidity describes any short- or long-term health problems that result from being pregnant or giving birth. Maternal mortality refers to the death of a woman from complications of pregnancy or childbirth that occur during

[1764] https://factor.niehs.nih.gov/2021/8/papers/dert/index.htm#a2
[1765] Gaskins AJ et al. Fertil Steril 2021;116(4):1052-1060. PMID: 34116830.
[1766] https://www.nichd.nih.gov/newsroom/news/020421-levonorgestrel
[1767] https://www.nichd.nih.gov/research/supported/cctn
[1768] World Health Organization. International statistical classification of diseases and related health problems, 10th revision (ICD–10). 2008 ed. Geneva, Switzerland. 2009.
[1769] https://www.cdc.gov/nchs/data/hestat/maternal-mortality/2021/maternal-mortality-rates-2021.htm

the pregnancy or within six weeks after the pregnancy ends. NIH supports research to improve understanding, early diagnosis, treatment, and prevention of pregnancy and birth complications, as well as to improve the data collected on maternal deaths and track general trends to inform research strategies.

Severe maternal morbidity (SMM), or unexpected life-threatening complications during delivery hospitalization, has increased in the U.S. since 2012.[1770] While the recurrence of several adverse pregnancy outcomes from one pregnancy to the next has been established, the recurrence risk of SMM is unknown. An NINR-funded population-based study linked vital statistics and hospital discharge records from California from 1997-2012 to determine whether women who have SMM in a first pregnancy are at increased risk of SMM in their second pregnancy. Findings indicate an approximate sixfold increased risk compared with women who did not have SMM in their first pregnancy. Based on the study's findings, health care providers may consider extra reproductive life planning discussions and very attentive inter-conception and prenatal care for women who experienced SMM at the time of their first birth.[1771]

The congressionally-mandated HHS Task Force for Research Specific to Pregnant Women and Lactating Women brought together clinical, research, advocacy, public health, regulatory, and pharmaceutical industry leaders, to address the significant gaps in research on safety, efficacy, and dosing of medications in pregnant and lactating women.[1772] The task force, which included the NIH and NICHD directors, converted its 15 recommendations of 2018 into multiple, concrete implementation steps for public- and private-sector action. These were submitted to the HHS Secretary in 2020.[1773]

Pregnancy is associated with a range of health concerns. The NHLBI Chronic Hypertension and Pregnancy trial examined the safety and effectiveness of using medication to treat mild hypertension in pregnancy, which is typically deferred for severe hypertension. Enrollment of 2,400 women of diverse race and ethnicity from 62 sites across the U.S.[1774] showed that targeting a blood pressure at a lower range (140/90 mm Hg rather than 160/105 mm Hg, as previously believed) was associated with a lower likelihood of the adverse outcomes.[1775]

Autoimmune diseases, in which the immune system mistakenly attacks a patient's body, are serious, chronic disorders that include type 1 diabetes, lupus, rheumatoid arthritis, and others. In the U.S., 80 percent of autoimmune disorders occur in women, and many of these women may become pregnant. To better understand obstetric and neonatal risks of these disorders, which can differ in symptoms and the tissues targeted by each disease, NICHD intramural researchers analyzed data from electronic medical records of 205,521 deliveries at 19 U.S. hospitals during 2002 to 2008. The researchers focused on several of the more common autoimmune disorders (type 1 diabetes, lupus, rheumatoid arthritis, multiple sclerosis, and Crohn's disease). They found that, despite the differences among the diseases, most were

[1770] Hirai AH, et al. JAMA Netw Open. 2022 Jul 1;5(7):e2222966. PMID: 35900764.
[1771] Bane S et al. Paediatr Perinat Epidemiol 2021;35(2):155-161. PMID: 33155710.
[1772] https://www.nichd.nih.gov/about/advisory/PRGLAC
[1773] https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations
[1774] https://clinicaltrials.gov/ct2/show/NCT02299414
[1775] Tita AT, et al. N Engl J Med. 2022 May 12;386(19):1781-1792. PMID: 35363951.

associated with an increased risk of preterm birth and other adverse pregnancy outcomes. Women with type 1 diabetes were at increased risk for nearly all problems studied, including respiratory distress syndrome (RDS) in infants, perinatal mortality, cesarean delivery, and preterm birth. Women with lupus or Crohn's were at risk for preterm delivery and RDS in their infants, while those with rheumatoid arthritis were at risk of their infants being small for gestational age. The findings highlighted the need for research to better understand immunologic function across pregnancy and its implications for prenatal care of women with autoimmune diseases and their infants.[1776]

Depression during pregnancy or after having a baby is one of the most common medical problems associated with pregnancy, and untreated depression can be harmful to a mother and to her child. Researchers analyzed data from more than 15,000 pregnancies based on whether the women were using low, medium, or high doses of antidepressants and whether they stopped taking the medicine during the first three months of pregnancy. The NICHD-supported study showed that medium doses taken throughout pregnancy slightly increased the risk of problems with the infant's heart structure. Medium or high doses taken throughout pregnancy increased the risk for preterm birth. All doses were associated with increased risk of breathing problems in the newborn, with higher doses more likely to result in such problems. Although these medications do present some risks for newborns, the results support using the lowest effective dose of antidepressants to help pregnant people with depression.[1777]

Capturing, utilizing, and sharing of data is vital in NIH's approach to addressing maternal health. In 2021, NICHD launched the Decoding Maternal Morbidity Data Challenge to help advance research on maternal health and promote healthy pregnancies. The goal of the challenge was to devise new ways of analyzing data from NICHD's Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be to identify factors that impact maternal morbidity and SMM so that clinicians can more quickly and accurately identify and treat pregnancy-related conditions, and therefore prevent severe illness or death for a pregnant person. Twelve prizes totaling $400,000 were awarded to seven winners who proposed innovative solutions to identify risk factors in first-time pregnancies. The winners of the challenge were announced in conjunction with the White House *Day of Action* on maternal health.[1778,1779]

Launched in 2020, NICHD's Maternal and Pediatric Precision in Therapeutics Hub program will provide pharmacology expertise, basic science research, and technology platforms for scientists conducting pharmacology research in obstetric participants.[1780,1781] In 2019, ORWH launched the *NIH Maternal Morbidity and Mortality (MMM) Web Portal*[1782] to provide trustworthy, science-based information on pre-pregnancy, healthy pregnancy, delivery, and post-pregnancy for scientists, researchers, consumers, and advocates. The portal is a central hub for resources on how NIH is approaching the public health issue of MMM. It provides information for researchers, scientists, clinicians, and the public, to enhance their

[1776] Williams A et al. J Autoimmun 2019;103:102287. PMID: 31147159.
[1777] Bandoli G et al. Pediatrics 2020;146(1):e20192493. PMID: 32513841.
[1778] https://www.nichd.nih.gov/research/supported/decodingmmdatachallenge
[1779] https://www.nichd.nih.gov/newsroom/news/120721-data-challenge-winners
[1780] https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint
[1781] https://grants.nih.gov/grants/guide/rfa-files/rfa-hd-21-026.html
[1782] https://orwh.od.nih.gov/mmm-portal/welcome-orwh

understanding of the complexities of MMM and to encourage the uptake of recommended evidence-based solutions, while promoting high-level dialogue between researchers, clinicians, and other advocates on maternal health-related calls to action.

In addition to expanding the use of data, NIH is fostering growth of other aspects of research infrastructure to drive the field of maternal health forward. The IDeA States Program builds research capacity in states that historically have had low levels of NIH funding, and it supports research that addresses the needs of medically underserved communities. ORWH partnered with NIGMS to bring women's health research to those parts of the country with the lowest levels of NIH funding.[1783] The resulting initiatives have expanded the research capacity of IDeA states to conduct research on women's health and disparities in states where women and children have poorer health outcomes.[1784,1785]

Environmental factors have been found to have an impact on maternal health and pregnancy outcomes. NIEHS-supported researchers have found that women living near natural gas and oil wells that use flaring to burn off excess gas face a 50 percent greater risk of premature birth than women with no such exposure. Babies born prematurely—before the 37th completed week of pregnancy—may suffer complications such as immature lungs, difficulty regulating body temperature, poor feeding patterns, and slow weight gain.[1786,1787]

This National Toxicology Program (NTP) recently released a report entitled, *Monograph on the Systematic Review of Traffic-related Air Pollution and Hypertensive Disorders of Pregnancy,*[1788] which suggests that traffic-related air pollution (TRAP) increases a pregnant person's risk for dangerous increases in blood pressure, known as hypertension. TRAP results from the combustion of fossil fuels by motor vehicles. NTP evaluated components of TRAP that included particulate matter, nitrogen oxides, carbon monoxide, black carbon, and elemental carbon, along with parameters such as traffic density and mothers' proximity to main roads. The report suggests that women who live within a quarter of a mile of a major roadway or in high traffic density regions may be at an increased risk for developing hypertensive disorders of pregnancy.

In addition to environmental factors, research implicates that other external factors influence pregnancy. To estimate national pregnancy-associated homicide mortality rates, NICHD-supported researchers examined mortality files from the National Center for Health Statistics from 2018 and 2019. There were 3.62 homicides per 100,000 live births among females who were pregnant or within one year postpartum, which was 16 percent higher than homicide prevalence among non-pregnant and non-postpartum females of reproductive age (with a homicide rate of 3.12 deaths per 100,000 population). Pregnancy and the postpartum period are times of elevated risk for homicide among all females of reproductive age,[1789]

[1783] https://www.nigms.nih.gov/News/results/Pages/20201009.aspx
[1784] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-20-017.html
[1785] https://grants.nih.gov/grants/guide/notice-files/NOT-GM-21-056.html
[1786] https://news.usc.edu/173335/natural-gas-flaring-pregnant-women-babies-health-risks-usc-research/
[1787] Cushing LJ et al. Environ Health Perspect 2020;128(7):77003. PMID: 32673511.
[1788] https://ntp.niehs.nih.gov/ntp/ohat/trap/mgraph/trap_final_508.pdf
[1789] Wallace M et al. Obstet Gynecol 2021;138(5):762-769. PMID: 34619735.

and there is a significantly elevated homicide risk in the African American and Black populations and among females aged 10-24, across racial and ethnic subgroups.

Racial and ethnic disparities in SMM have persisted and increased at high rates, according to an analysis of nearly 20 years of California hospital records, which was funded by NICHD. Known risk factors for these complications, such as blood pressure disorders, asthma, and Caesarean birth, do not fully explain the increase or why the disparities persist.[1790,1791] In September 2020, NINR held a virtual workshop on innovative models of care for reducing inequities in maternal health. The workshop explored how nurses, midwives, and birth companions can improve maternal and infant health, specifically for women in U.S. communities affected by structural and health inequalities.[1792,1793]

It is estimated that more than one million women of childbearing age in the U.S. have a disability, but little is known about their pregnancy risks or even their basic experiences during or after pregnancy. NICHD research interests overlap with the focus of the Pregnancy Risk Assessment Monitoring System (PRAMS), a CDC survey administered by state health departments, which includes information on mothers' attitudes and experiences before, during, and shortly after pregnancy. Topics include pregnancy, breastfeeding, infant health care, and contraception. NICHD's efforts to include data on women with disabilities will contribute important information on the impact of disability on pregnancy and maternal and child health. NICHD is providing $1.5 million to incorporate a disability survey as a supplement to the PRAMS questionnaire, as part of data collection in 22 states. The survey consists of six questions on functions, including seeing, hearing, walking, and self-care.[1794]

People who are deaf or hard of hearing (DHH) are at risk for poorer health outcomes, in part due to communication barriers that hinder access to health care services and information. NICHD-supported researchers compared pregnancy complications, birth characteristics, and neonatal outcomes between DHH and non-DHH women in Massachusetts. They found that DHH women had an increased risk for many chronic medical conditions and pregnancy complications, including pre-existing diabetes, chronic hypertension, gestational diabetes, pre-eclampsia and eclampsia, placental abruption, cesarean delivery, severe bleeding, and infection. Deliveries to DHH women were also significantly associated with increased risk adverse outcomes for the fetus, including preterm birth, low birth weight, and poor Apgar scores.[1795,1796]

[1790] https://www.nih.gov/news-events/news-releases/rate-life-threatening-childbirth-complications-increasing-sharply-across-us-racial-ethnic-groups
[1791] Leonard SA et al. Ann Epidemiol 2019;33:30-36. PMID: 30928320.
[1792] https://videocast.nih.gov/watch=38172
[1793] https://www.ninr.nih.gov/sites/files/docs/MaternalHealthWorkshop_Summary_508c.pdf
[1794] https://www.nichd.nih.gov/newsroom/news/110118-PRAMS
[1795] Mitra M et al. Am J Prev Med 2020;58(3):418-426. PMID: 31952943.
[1796] Mitra M et al. Womens Health Issues 2021;31(5):470-477. PMID: 33888398.

Fetal and Infant Health

The health of mother and child are closely intertwined. This section will spotlight some of NIH's recent research focused on aspects of fetal and infant health. Additional research on child health is covered in the Life Stages, Human Development, and Rehabilitation section of this chapter.

The NICHD's Maternal-Fetal Medicine Units (MFMU) Network is designed to conduct clinical trials in maternal-fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. Established in 1986, the network aims to reduce maternal, fetal, and infant morbidity related to preterm birth, fetal growth abnormalities, and maternal complications, and to provide the rationale for evidence-based, cost-effective obstetrics practice. More than 50 randomized clinical trials, cohort studies, and registries have been completed or are in progress. Current projects include randomized controlled trials of preventing congenital cytomegalovirus infection, testing whether pravastatin can prevent preeclampsia, identifying risk factors for perinatal transmission of hepatitis C virus infection during pregnancy, and evaluating the effectiveness of individualized opioid prescriptions after cesarean delivery. Completed projects include randomized controlled trials on fetal heart rate monitoring, treating sleep apnea in pregnancy, preventing preterm birth, preventing obstetrical hemorrhage after cesarean delivery, preventing effects from cytomegalovirus infection, and preventing preeclampsia. Studies in the MFMU also found that COVID-19 infection increases risk of pregnancy complications, preterm birth, and maternal death. COVID-19 vaccines can confer immunity from women to their newborns through the placenta or breastmilk.[1797,1798,1799,1800]

NICHD intramural researchers conduct clinical and basic research in perinatal medicine and related disciplines with the goal of developing novel diagnostic, therapeutic, and preventive strategies to reduce adverse pregnancy outcomes and infant morbidity and mortality and to train healthcare professionals in perinatal medicine and related disciplines. This NICHD intramural group discovered that the placenta lacks the major molecules used by the SARS-CoV-2 virus to cause infection, which may help to explain why the virus has rarely been found in fetuses or newborns of women with COVID-19. These researchers played a key role in proposing a standardized definition of placental SARS-CoV-2 infection, offering guidance for the best methods to evaluate placental SARS-CoV-2 infection for research and clinical applications, in order to help streamline research on SARS-CoV-2 infection during pregnancy and ultimately optimize clinical care.[1801,1802,1803]

[1797] https://www.nichd.nih.gov/research/supported/mfmu
[1798] https://www.nichd.nih.gov/newsroom/news/032921-COVID-vaccine-pregnancy
[1799] https://www.nichd.nih.gov/newsroom/news/012821-GRAVID
[1800] https://www.nichd.nih.gov/newsroom/news/020722-COVID-19-pregnancy-complications
[1801] https://www.nih.gov/news-events/news-releases/placenta-lacks-major-molecules-used-sars-cov-2-virus-cause-infection
[1802] https://www.nih.gov/news-events/news-releases/nih-convened-expert-panel-proposes-standardized-definition-placental-sars-cov-2-infection
[1803] Roberts DJ et al. Am J Obstet Gynecol 2021;225(6):593.e1-593.e9. PMID: 34364845.

Other NICHD-supported researchers are also focusing their efforts on the placenta. They found that episodes of maternal stress or depression during pregnancy are associated with chemical modifications to placental genes. The modifications involve DNA methylation (binding of compounds known as methyl groups to DNA), which can alter a gene's activity. Some of the methylation changes associated with maternal depression occurred near genes involved in brain development, suggesting that maternal depression in pregnancy could have long-term implications for the mental development of the child.[1804,1805]

Research has shown that sleep disorders during pregnancy can adversely impact maternal and child health. In a study supported by NHLBI and NICHD, of 1.4 million maternal and newborn records, investigators found that children born to mothers with sleep apnea during pregnancy were more likely to have birth defects, be admitted to neonatal ICU, or require resuscitation at birth. The Sleep Disordered Breathing, Obesity and Pregnancy Study trial, funded by NHLBI and NICHD is now investigating whether treating sleep apnea among pregnant people can improve outcomes for mother and child.[1806,1807]

In pregnant people, polyunsaturated fatty acids and their metabolic derivatives called eicosanoids are associated with infant size at delivery, according to NIEHS scientists and their collaborators. This research also provides novel longitudinal characterization of eicosanoids in blood plasma during different gestational ages of pregnancy. Certain eicosanoids, which are known to derive from inflammatory processes from these fatty acids, were found to be exclusively higher in pregnancy cases, which resulted in low birth weight.[1808,1809]

Preterm births are the leading cause of neonatal illness and death. However, there is currently a dearth of options for predicting and treating this public health problem. Scientists funded by NINR have compared the cervicovaginal microbiota of women who had spontaneous preterm births versus women delivering at term, to better understand whether the microbial environment is a factor. In the study, seven bacteria were found to significantly increase the risk of preterm births, with a stronger effect seen in African American women. They also found that higher levels of an antimicrobial produced by the immune system lowered the risk of preterm birth, also with a greater effect in African American women.[1810]

In 2021, NICHD hosted a workshop on *Breastmilk Ecology: Genesis of Infant Nutrition,* which focused on gaining a better understanding of the biology of human milk in order to address ongoing and emerging questions about infant feeding practices. A group of researchers, including scientists at NICHD, issued a funding announcement directed at encouraging research on understanding human breastmilk as a biological system. This means evaluating all the components in breastmilk, its nutrients as well as its immune factors and other bioactive elements, at the various stages of lactation—from the first minutes

[1804] https://www.nichd.nih.gov/newsroom/news/100621-depression-pregnancy
[1805] Tesfaye M et al. Epigenomics 2021;13(18):1485-1496. PMID: 34585950.
[1806] https://clinicaltrials.gov/ct2/show/NCT02086448?cond=disordered%2Bbreathing%2Bin%2Bpregnancy
[1807] Bourjeily G et al. Sleep Med 2020;66:233-240. PMID: 31981755.
[1808] https://factor.niehs.nih.gov/2020/10/papers/dir/index.htm#a2
[1809] Gaskins AJ et al. Fertil Steril 2021;116(4):1052-1060. PMID: 34116830.
[1810] Elovitz MA et al. Nat Commun 2019;10(1):1305. PMID: 30899005.

after birth to the age when children typically begin to eat other foods. Such a comprehensive study of breastmilk can help researchers provide the evidence to inform policymakers and develop better ways to optimize child health from infancy. In addition, NICHD's Pediatric Trials Network is assessing the safety of drugs passed through breastmilk.[1811,1812,1813]

Emerging Technologies

Progress is often limited by the tools that are available, so for biomedical and behavioral research to flourish, advances in technology are crucial. As new tools and technologies are developed, new research areas emerge, and the biomedical research enterprise moves forward. NIH supports cross- and inter-disciplinary research and collaborations across cell biology, physics, engineering, and computer science, among others, to contribute to increasing understanding of health and disease, while moving toward improved therapeutics and quality of life.

Summary

Many research fields have been transformed by technological innovation and the development of new tools and techniques. The development of such cutting-edge technologies is supported across NIH, and it contributes to drive the broader biomedical and behavioral research enterprise forward. NIH funds and conducts research on innovative tools that facilitate biomedical research across the research continuum outlined in Chapter 2. These tools range from those with real-world application (e.g., point-of-care technologies) to those that change our understanding of how cells function (e.g., microscopy and imaging innovations). This also includes innovations in tools with clinical implications, such as novel ways to grow stem cells and tissue chips, among the many other recent examples outlined in this section.

The NIGMS Technology Development Program provides funding opportunities to support the development of new technology that will enable future acquisition of new biomedical knowledge.[1814] The funding opportunities are intended for small, exploratory projects to evaluate the feasibility of concepts and explore ideas that have not yet been realized. The funding also supports focused technology development to create functional prototypes based on feasible concepts. Applications are evaluated on the likelihood of creating enabling biomedical technologies. These opportunities support concepts and prototypes that can be validated to work but are not yet ready to be used by the biomedical community to acquire new biomedical knowledge. So far, these funding opportunities have attracted novel proposals to build new microscopes and analytical technologies for understanding molecular structure and dynamics, as well as for new molecular techniques to alter proteins and genes to reveal normal function and develop new molecular tools.

NIH also supports early-stage research and development in the private sector through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs by providing more than $1.2 billion in funding annually. These programs have demonstrated significant impact in economic

[1811] https://www.nichd.nih.gov/about/meetings/2021/011521
[1812] https://pediatrictrials.org/tag/cuddle/
[1813] Christian P et al. Am J Clin Nutr 2021;113(5):1063-1072. PMID: 33831952.
[1814] https://www.nigms.nih.gov/about/overview/BBCB/biomedicaltechnology/Pages/technologydevelopment.aspx

output and healthcare benefit.[1815] However, commercialization of products can be difficult to navigate, particularly for new entrepreneurs. NIH has a comprehensive Technical and Business Assistance (TABA) program intended to help small businesses identify and address their most pressing product development needs.[1816] Through the TABA Needs Assessment program, NIH provided third-party unbiased assessments of progress in technical and business areas that are critical to success in the competitive health care marketplace. In FY 2019–2021, 190 needs assessments were completed.

Further illustrative of NIH's commitment to advancing biomedical research through the funding of new technologies, NIH funding for Biotechnology was $7,219 million in FY 2019, $7,767 in FY 2020, and $7,847 million in FY 2021; funding for Bioengineering was $5,091 million in FY 2019, $5,646 million in FY 2020, and $5,720 million in FY 2021; and funding for Biomedical Imaging increased from $2,352 million in FY 2019 and $2,544 million in FY 2020 to $2,774 million in FY 2021.

Several technology fields where recent notable advancements have been made are outlined in the following subsections, and some examples appear in other sections of Chapter 3.

Point-of-Care and Wearable Technology

Point-of-Care Technology

Technologies that improve diagnostics and treatment are becoming more accessible and available directly at the point of care. Improving communication between patient and provider is one area in which technological advancement can play a role in improving health outcomes. Barriers to effective patient–provider communication can lead to significantly poorer medical outcomes, lower patient satisfaction with care, and increased staff stress. For example, some patients are unable to use the hospital's nurse call system due to hearing loss, mechanical ventilation, a motor-speech impairment, or a language barrier. With the support of SBIR funding from NINR, Iowa Adaptive Technologies (business name Voxello®) developed the noddle® switch and noddle-chat™ tablets to address communication barriers and to provide hospitals with a relatively simple system that can be rapidly deployed in acute-care settings.[1817,1818] The noddle uses patented gesture-detecting algorithms to identify a patient's smallest intentional gesture, such as a tongue click, head nod, or finger tap, to activate a hospital's nurse call system. The noddle-chat communication tablet generates a synthesized voice allowing patients to communicate with others and actively engage in their care. After commercialization, Voxello's technology has been used with adult and pediatric patients at 15 medical centers across the U.S.

In a related advancement, scientists supported by NIDCD who study voice research have developed a personalized text-to-speech augmentative and alternative communication (AAC) device called VocaliD.[1819] This device blends the speech of two individuals, that of a donor and a recipient, to recreate the recipient's natural voice. A donor voice is matched with a recipient in terms of gender, age, region of origin, and other characteristics to produce a more personalized synthetic voice. By commercializing VocaliD, NIDCD-funded scientists have refined the technology, automating certain steps, and making the entire process

[1815] https://www.nationalacademies.org/our-work/assessment-of-the-sbir-and-sttr-programs-at-nih
[1816] https://seed.nih.gov/support-for-small-businesses/technical-business-assistance-program
[1817] Hurtig RR, et al. *Perspect ASHA Spec Interest Groups*. 2019 Oct;4(5):1017-1027. PMID: 34113718.
[1818] https://seed.nih.gov/portfolio/stories/Iowa-Adaptive
[1819] https://vocalid.ai/about-us/TED talk "Synthetic Voices, as unique as fingerprints"

of creating personalized, synthetic voices faster and more efficient. These improvements will advance speech synthesis while humanizing machine-mediated spoken interaction for AAC devices and other technologies.

In another project supported by SBIR funding, NCATS awarded Lyndra Therapeutics funding to help develop and move toward commercializing a solution that could address the problem of patients not taking medicine as prescribed,[1820] by "changing the pill instead of the patient."[1821] In the U.S. alone, not taking medication as prescribed contributes to 125,000 preventable deaths, 50 percent of treatment failures, and 25 percent of hospitalizations, at a cost between $100 billion and $289 billion each year.[1822] The solution that the Lyndra team created was a dosage form that, to patients, looks like the familiar drug capsule. Once the capsule reaches the stomach, however, it blossoms into a star shape that is too large to pass through the valve that opens into the intestines–yet it does not block food from passing through. This allows the dosage form to remain in the stomach, releasing a slow, steady dose of medicine, until the material breaks down and exits via the gastrointestinal tract, like undigested food. This new type of pill could allow medication to remain in the stomach for up to a week, greatly reducing the number of pills a patient is required to take, down to potentially a single dose.

As with changes to the drug technology itself, NIH has made treatment technology available and accessible outside of hospital settings. Through SBIR funding, researchers have developed a device designed to alleviate stress in the treatment of neonatal jaundice: they made the treatment device portable. Severe neonatal jaundice is one of the most common reasons that newborns remain in or are readmitted to the hospital. Without adequate treatment, newborns with neonatal jaundice are at risk of developing permanent brain damage that can result in cerebral palsy, deafness, and vision impairment. However, the treatment (high-intensity blue-light phototherapy) usually takes place in a specialized neonatal intensive care unit (NICU), which interferes with parent-child bonding, causes stress for the family, and increases healthcare costs. With small business funding from NICHD and FDA approval, the bili-hut™ now offers portable phototherapy for neonatal jaundice that can be used at the parent's bedside at home or in a hospital, reducing healthcare costs and keeping newborns and their families together during treatment.[1823]

NIH also supports innovation in point-of-care technology by facilitating the research of undergraduates. Through the Design by Biomedical Undergraduate Teams (DEBUT)[1824] Challenge, undergraduate student teams work to develop technology solutions for unmet needs in any area of healthcare. The top prize in 2021 went to a team from the University of South Florida for their invention called the Eucovent, a ventilator add-on that allows multiple patients to be ventilated with a single ventilator.[1825] This ventilator device addresses some of the safety concerns traditionally associated with co-ventilation, and the device

[1820] https://seed.nih.gov/portfolio/stories/Lyndra
[1821] https://ncats.nih.gov/pubs/features/changing-the-pill-tackling-medication-adherence-through-innovative-technology
[1822] Viswanathan M, et al. *Ann Intern Med.* 2012 Dec 4;157(11):785-95. PMID: 22964778.
[1823] https://www.nichd.nih.gov/grants-contracts/SBIR_STTR/showcase/bili-hut
[1824] https://www.nibib.nih.gov/research-programs/DEBUT-challenge
[1825] https://www.nibib.nih.gov/news-events/newsroom/debut-challenge-awards-prizes-future-bioengineers

can be used in low-resource scenarios, such as rural areas, military settings, and natural disaster scenarios, making ventilation more accessible.

Improving health technology also requires investment in research to study the development, validation, feasibility, and effectiveness of innovative mobile health (mHealth) interventions or tools. These tools are especially suited for low- and middle-income countries (LMICs) that utilize new or emerging technology, platforms, systems, or analytics. [1826] FIC supports research that seeks to catalyze innovation through multidisciplinary research that addresses global health problems, develop an evidence base for the use of mHealth technology to improve clinical and public health outcomes, and strengthen mHealth research capacity in LMICs.

Wearable Technology

Innovations in wearable technology open avenues for noninvasive health monitoring and improvements in treatments for movement disorders. Wearable technology has become a common feature in many people's lives, and this creates the possibility to capitalize on people's routine usage to improve health. With the widespread use of wearable pedometers, for example, daily step count has become more of a focus for health. NIH-supported researchers found that a greater number of daily steps was significantly associated with lower all-cause, cardiovascular disease, and cancer mortality in adults who were at least 40 years of age.[1827] These results provide evidence for the health benefits associated with physical activity and show how that activity can be monitored via a wearable pedometer.

Health monitoring is another area of health care that is historically associated with invasive tools. NIBIB-funded engineers have developed a flexible epidermal patch that can simultaneously and continuously monitor cardiac output and metabolic levels of glucose, lactate, caffeine, or alcohol.[1828] The patch is a major step towards continuous non-invasive health monitoring.

In addition to health monitoring, improvements in wearable technology have allowed researchers to develop noninvasive tools to help treat movement disorders such as cerebral palsy (CP). CP is the most common movement disorder that affects children. It often results in a debilitating crouch gait or persistent bending of the legs. Children who walk with a crouch gait pattern frequently experience a decline in function as they age because their strength and coordination cannot keep up with the extra demands this pattern places on their muscles. NIH researchers developed the first robotic exoskeleton to alleviate crouch gait in children, and unlike existing exoskeletons, which guide the users' limbs through predefined movements, the NIH device provides precisely timed bursts of assistance to extend the limb, but then turns these off, forcing the user to maintain and adjust their muscle activity while using the exoskeleton.[1829] When using this new device and approach, children's crouch gait improved and their step length and gait speed also increased. This technology opens avenues of research that could support

[1826] https://www.fic.nih.gov/Programs/Pages/mhealth.aspx
[1827] Saint-Maurice PF, et al. *JAMA*. 2020 Mar 24;323(12):1151-1160. PMID: 32207799.
[1828] Sempionatto JR, et al. *Nat Biomed Eng*. 2021 Jul;5(7):737-748. PMID: 33589782.
[1829] Shideler BL, et al. *J Neuroeng Rehabil*. 2020 Sep 3;17(1):121. PMID: 32883297.

training users of the technology to experience an improved walking pattern even when the user is not wearing the device.

Computational Technology

As a result of recent scientific advances, a tremendous amount of data are available from biomedical research and clinical interactions with patients, health records, clinical trials, and adverse-event reports, which could be useful for understanding health and disease and for developing and identifying treatments for diseases. NIH invests in cutting-edge computational technologies that are designed to catalyze health research by using this abundance of data. However, these very rich, yet different data sources are housed in various locations, often in forms that are not compatible or interoperable with each other. To address these problems, NCATS launched the Biomedical Data Translator program, called "Translator" for short.[1830] This multiyear, iterative effort will culminate in the development of a comprehensive, relational, N-dimensional biomedical data Translator that integrates multiple types of existing data sources, including objective signs and symptoms of disease, drug effects, and intervening types of biological data relevant to understanding pathophysiology.

Another investment in connecting data from different sources is from the NIH Common Fund Human BioMolecular Atlas Program (HuBMAP).[1831] Researchers developed a process that connects DNA, RNA, chromatin, and protein data from separate experiments, then an algorithm "anchors" the data together, generating a link between two datasets.[1832] This anchoring allows the researchers to identify known or unexpected types of cells in a tissue. By joining these data together, this new computational method has given researchers a novel tool to help build more complete biological atlases, leading the way to more discoveries about the intricacies of human cells and tissues.

[1830] https://ncats.nih.gov/translator/about
[1831] https://commonfund.nih.gov/hubmap/highlights
[1832] Stuart T, et al. *Cell*. 2019 Jun 13;177(7):1888-1902.e21. PMID: 31178118.

Figure 43: Dr. Sameer Antani conducting AI/ML Research for Clinical Medical Image Processing. Credit: NLM OCPL video team

NIH is also supporting the development of machine learning (ML) and Artificial Intelligence (AI/ML) approaches that can improve analysis of biomedical images. NLM researchers are conducting AI/ML research to develop algorithms to analyze biomedical images in support of health screening and research. Specific work focuses on drug-resistant tuberculosis,[1833,1834] malaria,[1835,1836] craniofacial images,[1837] cervical cancer,[1838] and COVID-19,[1839] where imaging plays a key role in diagnostic decision making and biomedical research. In addition, NIH assembled a public meeting with radiology societies and other members of the community to map a path forward for translational research on AI in medical imaging.[1840] That meeting resulted in a report that identifies research priorities that leverage big data, the cloud, and ML for augmenting the clinicians' diagnoses, and assessing the patients' responses to therapy, all of which will be used to guide innovation into the future.

Microscopy and Imaging

NIH-supported researchers are developing cutting-edge imaging technologies that are able to view single molecules and DNA within cells, take images of the full human body, and observe real-time changes within organs and organ systems. Advances in imaging technology allow for better diagnostics and treatments and can improve our understanding of basic cellular function. Cellular imaging has had a significant impact

[1833] Yang F, et al. *Quant Imaging Med Surg*. 2022 Jan;12(1):675-687. PMID: 34993110.
[1834] Rajaraman S, et al. *IEEE Access.* 2020;8:115041-115050. PMID: 32742893.
[1835] Kassim YM, et al. *IEEE J Biomed Health Inform*. 2021 May;25(5):1735-1746. PMID: 33119516.
[1836] Yu H, et al. *BMC Infect Dis*. 2020 Nov 11;20(1):825. PMID: 33176716.
[1837] Kim I, et al. *Annu Int Conf IEEE Eng Med Biol Soc*. 2020 Jul;2020:1294-1298. PMID: 33018225.
[1838] Guo P, et al. *J Clin Med*. 2021 Mar 1;10(5):953. PMID: 33804469.
[1839] Rajaraman S, et al. *PLoS One*. 2020 Nov 12;15(11):e0242301. PMID: 33180877.
[1840] Allen B Jr, et al. *J Am Coll Radiol*. 2019 Sep;16(9 Pt A):1179-1189. PMID: 31151893.

on biological research and our understanding of interactions between molecular components within the cell as well as the dynamics of single molecules in both normal and abnormal cells.

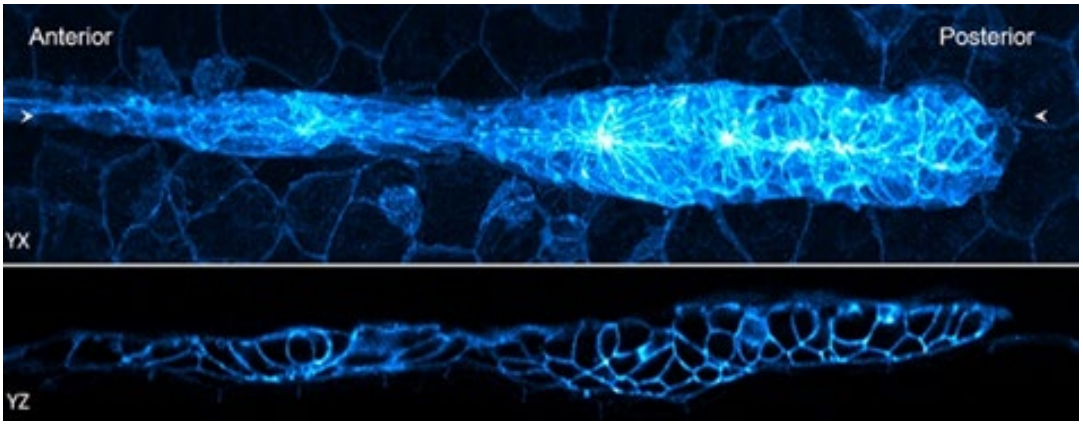


Figure 44: Blue fluorescent cells. Credit: Hari Shroff Lab, NIBIB

Figure 45: Nanopore sequencing. Credit: National Human Genome Research Institute

In the NHGRI Genome Technology (GTP)[1841] program, NIH supports research to innovate and develop new methods, technologies, and systems that enable rapid, low-cost determination of nucleic acid sequence and genotyping along with epigenetic, functional, and synthetic genomics experiments. In 2019, GTP-funded research yielded an entirely new type of microscopy, DNA microscopy, that allows for the simultaneous visualization of the sequence and location of nucleic acids within a cell, which will be useful for studying diverse cell types.[1842] The GTP has supported key work leading to profound decreases in the cost of DNA sequencing and the widespread commercialization and dissemination of new technologies.[1843] The increased accessibility of genome sequencing technologies has revolutionized the study of human genomic variation and its relationship to disease.

At the larger, body-system level, imaging technologies have been developed to improve non-invasive diagnostic and monitoring techniques. Optical coherence tomography (OCT) is a non-invasive imaging technique that is analogous to ultrasound imaging, but instead of using sound waves and their reflections to visualize tissues inside the body, researchers use near-infrared light.[1844] When diagnosing middle ear infections, a clinician using this technique is able to obtain images beyond the eardrum and see if fluid has built up in the middle ear cavity or if a biofilm has developed. If a biofilm has developed, a clinician may opt for surgical treatment, and OCT can assist in that assessment. NIH-supported research has also led the development of a more portable OCT machine, increasing its utility in clinical settings.[1845]

At the full-body scale, researchers supported in part by an NIH Common Fund Transformative Research award,[1846] have created the first 3D, full-body imaging device.[1847,1848] This device, called EXPLORER (Extreme Performance Long axial Research scanneR) total-body PET scanner, will allow researchers and clinicians to visualize multiple organs at once, and create movies to show dynamic changes over time. Eventually, this technology could be used in wide-ranging clinical and research applications, including those studying inflammation, tracking infections, diagnosing cancer, and exploring interactions between different organ systems.

To address challenges in linking local circuit function to global brain activity, researchers funded by NINDS and the NIH BRAIN Initiative unified two technologies, two-photon microscopy and mesoscopic imaging, to simultaneously measure microcircuit activity of single neurons and the meso-scale activity in the mouse cortex.[1849] Researchers leveraged their new tool to examine local and large-scale connections in the somatosensory cortex. This powerful, multi-scale imaging tool will accelerate our ability to measure and understand brain architecture and function across scales. In another BRAIN Initiative-funded innovation, researchers developed a new MRI methodology that measures changes in tissue stiffness in real time and

[1841] https://genometdcc.org/
[1842] Weinstein JA, et al. *Cell*. 2019 Jun 27;178(1):229-241.e16. PMID: 31230717.
[1843] https://www.genome.gov/Funded-Programs-Projects/Genome-Technology-Program
[1844] https://www.nibib.nih.gov/news-events/newsroom/when-it-comes-innovation-researcher-all-ears
[1845] Won J, et al. *Biosensors (Basel)*. 2021 May 3;11(5):143. PMID: 34063695.
[1846] https://commonfund.nih.gov/tra
[1847] Zhang X, et al. *Proc Natl Acad Sci U S A*. 2020 Feb 4;117(5):2265-2267. PMID: 31964808.
[1848] Badawi RD, et al. *J Nucl Med*. 2019 Mar;60(3):299-303. PMID: 30733314.
[1849] Barson D, et al. *Nat Methods*. 2020 Jan;17(1):107-113. PMID: 31686040

is 60 times faster than previous methods.[1850] This new technique has the potential to shed light on altered neuronal activity in brain diseases.[1851]

Cell Cultures and Tissue Chips

A critical component to being able to understand cellular function, and to be able to test the impact and efficacy of treatments on cells before moving to organisms, is the ability to grow and maintain cell lines in a laboratory setting. Human-induced pluripotent stem cells (hiPSCs) have tremendous translational potential because they are derived from reprogrammed skin or blood cells. These hiPSCs can, in theory, grow forever, therefore serving as an inexhaustible source for specialized cells, such as brain, kidney and heart cells. However, hiPSCs are challenging to work with because manual culture is variable and labor-intensive. Additionally, stem cells are sensitive, so their potential uses in medicine are hampered by the stress of growing in a cell culture dish, which can damage their DNA and lead to cell death. To address the variability and high labor needs in hiPSC cell cultures, NCATS IRP researchers established a robotic platform compatible with 2D and 3D culture formats that automates hiPSC culture and differentiation.[1852] This approach allows for rapid and standardized manufacturing of billions of hiPSCs that can be produced in parallel from up to 90 different patient- and disease-specific cell lines. This robotic cell culture platform has the potential to make hiPSC biomanufacturing and differentiation processes reproducible, scalable, and standardized. NIH-supported researchers have also devised a four-part small-molecule cocktail that can protect hiPSCs from stress and maintain normal stem cell structure and function.[1853] Scientists at the Stem Cell Translation Laboratory tested thousands of compounds and drugs to identify a unique combination that greatly improved stem cell survival and reduced cell culture stress. These two technologies will change how researchers can utilize stem cells and could enhance the potential therapeutic uses of stem cells, ranging from treating diseases and conditions, such as diabetes, Parkinson's disease and spinal cord injury, to genome editing.

Additional research on cell culture technology is being done to address the challenge presented by the fact that traditional drug development uses cellular assays in which cells are grown in 2D plastic surfaces that do not mimic the native environment of cells in tissues and organs. Since these cellular assays are not like human tissues, the efficacy and toxicity of potential new drugs tested in these 2D assays differ from that in real tissues. To improve the predictive success of preclinical drug development, the NCATS 3D Tissue Bioprinting group used innovative tissue engineering techniques to develop human skin tissue equivalents with cellular and physiological complexity that mimics the environment of cells in the body.[1854,1855] The approach is scalable to multi-well plates, and it provides a platform for topical and systemic drug discovery. These innovative tissue models could help scientists better predict the way patients will respond to potential new therapeutics.

[1850] Patz S, et al. *Sci Adv*. 2019 Apr 17;5(4):eaav3816. PMID: 31001585.
[1851] https://www.nibib.nih.gov/news-events/newsroom/imaging-brain-thinking-using-new-mri-technique
[1852] Tristan CA, et al. *Stem Cell Reports*. 2021 Dec 14;16(12):3076-3092. PMID: 34861164.
[1853] Chen Y, et al. *Nat Methods*. 2021 May;18(5):528-541PMID: 33941937.
[1854] Wei Z, et al. *Front Bioeng Biotechnol*. 2020 Feb 21;8:109. PMID: 32154236.
[1855] Liu X, et al. *Biofabrication*. 2020 Apr 9;12(3):035002. PMID: 32059197.

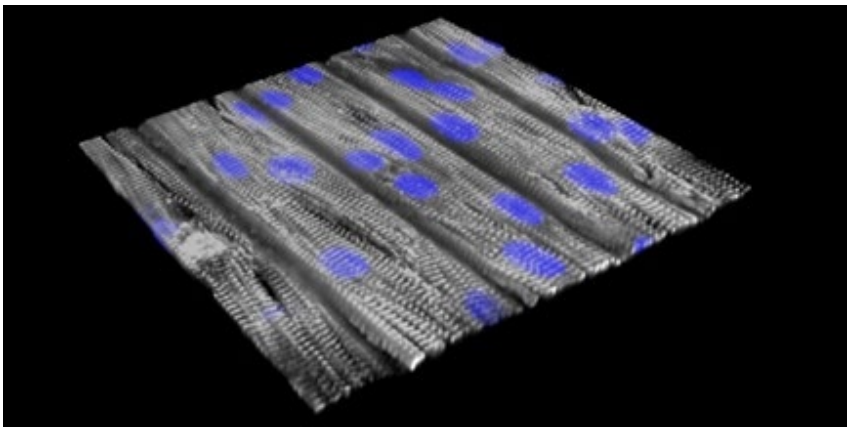


Figure 46: A tissue model of catecholaminergic polymorphic ventricular tachycardia (CPVT), a leading cause of sudden death from cardiac arrest in children and young adults, on a tissue chip. Cardiomyocytes (heart muscle cells) carrying CPVT mutations, which were seeded onto an engineered surface. The cells, shown in purple, lined up in a direction similar to how heart muscle is organized and beat together. Credit: Sung Jin Park/Boston Children's Hospital and Donghui Zhang/Harvard SEAS

Tissue chips are another 3D device made to support living human tissues and cells. Tissue chips are designed as accurate models of the structure and function of human organs, such as the lungs, liver, and heart. Approximately 85 percent of late-stage clinical trials of candidate drugs fail because of drug safety problems or ineffectiveness, despite promising preclinical test results.[1856] To help improve the design and implementation of clinical trials, NIH supports researchers using tiny, bioengineered models of human tissues and organ systems to study diseases and test drugs. The Clinical Trials on a Chip initiative will lead to more informative and efficient clinical trials for both common and rare diseases. NCATS is also exploring the use of tissue chips in space, which promises to speed researchers' understanding of diseases and their search for potential treatments.[1857] In collaboration with the ISS National Lab, the Tissue Chips in Space initiative supports tissue chip research projects in space to accelerate scientists' exploration of everything from why immune systems change with age to how muscle fibers weaken over time, which may speed the delivery of effective prevention and treatment options to patients in need.[1858,1859] On Earth, certain diseases and aging processes take years to develop. In microgravity, those same health conditions progress in only weeks or months, making the ISS National Lab a unique environment to study diseases and potential treatments on a faster timeline.

[1856] https://ncats.nih.gov/news/releases/2020/nih-awards-tiny-bioengineered-organ-models-to-improve-clinical-trials-development-and-design
[1857] https://ncats.nih.gov/tissuechip/projects/space
[1858] https://ncats.nih.gov/news/releases/2019/tissue-chips-in-space
[1859] https://ncats.nih.gov/news/releases/2020/NIH-Funded-Tissue-Chips-in-Space

Figure 47: Lung-bone Marrow Tissue ChipA lung-bone marrow tissue chip in space will help researchers explore how the body fights infection. Credit: NCATSBIOLines Laboratory, University of Pennsylvania

Cellular Function

Understanding how DNA, RNA, and cellular structures work together in cellular functions is critical to understanding cellular dysfunction and developing treatments, including those focused on gene editing, for diseases. To better understand cellular structure and function, the NIH Common Fund's 4D Nucleome (4DN) program supports researchers who are studying the three-dimensional organization of the nucleus in space and time (the 4th dimension).[1860] The nucleome is the molecular contents of the cell's nucleus, including DNA, the genetic blueprint of life. In phase 1, new technology and resources were made publicly available for the study of the nucleome organization in single cells. phase 2 has a growing emphasis on the role of the nucleome in human health and disease. One example of an advancement developed within the 4DN consortium is a new sequencing technique that enables researchers to map the location of every gene in DNA, relative to other marked molecular structures (tyramide signal amplification sequencing, TSA-Seq). [1861] This advance can help show how the position of a gene in the nucleus might affect the gene's activity.

In addition to better understanding the structure of the cell and genes within the cell, scientists supported by NIH have been investigating RNA and its role in cellular function. Significant progress was made in the first stage of the NIH Common Fund Extracellular RNA Communication (ExRNA) program,[1862] which explored the role the biological molecule RNA plays in cell-to-cell communications when it is transported between cells. The ExRNA program[1863] published a package of papers in the *Cell* family of journals that detailed new findings about RNA transported between cells and the bubble-like vesicles that can carry it

[1860] https://commonfund.nih.gov/4DNucleome
[1861] Chen Y, et al. *J Cell Biol*. 2018 Nov 5;217(11):4025-4048. PMID: 30154186.
[1862] https://commonfund.nih.gov/Exrna/
[1863] https://commonfund.nih.gov/exrna

to molecules like RNA from cell to cell throughout the body.[1864] Among the many published results is the serendipitous discovery that proteins carried inside tiny, bubble-like vesicles, called exosomes, may influence a cancer's response to immunotherapy. It is now better appreciated that there is a surprising amount of complexity both in the types of carriers that transport exRNA molecules between cells and in the different types of exRNA molecules associated with the carriers.

As cellular structure, DNA, and RNA are better understood, it opens avenues of research that are focused on gene editing approaches. NIH Common Fund's Somatic Cell Genome Editing program (SCGE) is working to improve the efficacy and specificity of gene editing approaches to help reduce the burden of common and rare diseases caused by genetic changes.[1865] SCGE-funded researchers published a collection of papers in the *Nature* family of journals on the genome editing approaches they were developing to help reduce the burden of disease caused by genetic changes.[1866,1867] The collection showcased the work of SCGE researchers and provided resources to explore the program's data and analyses. This included work on biological systems and models, genome editing platforms, and systems to deliver editors to the correct cells. In Fall 2019, the program launched a phase 2 to accelerate the development of genome editing therapeutics by funding studies to enable Investigational New Drug (IND) applications, establishing pathways to regulatory approval, and disseminating successful strategies for initiating first-in-human clinical trials.

Beyond gene editing, researchers supported by an NIH Common Fund Transformative Research Award built a synthetic DNA code using eight amino acid building blocks, instead of the four amino acids used in DNA found in nature.[1868] This synthetic DNA may have potential applications for information storage, novel diagnostic and therapeutic applications, and may even provide clues about the search for life forms beyond Earth. It is an area ripe for future research and applications.

Other Innovations

As nanotechnology becomes more prevalent, and computer microchips need smaller and smaller parts, the ability to develop structures on that smaller scale becomes even more critical. An NIH-funded research team developed a novel technology to create nanoscale 3D objects using a material commonly found in disposable diapers.[1869] Using polyacrylate gel as a scaffold, researchers were able to attach materials in precise locations within the gel, which can then be shrunken by applying acid. This technique, called Implosion Fabrication, may be used in optics, nanoscale electronics, or robotics.

To further drive nanoscale innovation, NIH-supported researchers have been studying the *Geobacter sulfurreducens* bacterium, which uses the biological equivalent of nanowires to conduct electricity.[1870] It does this to survive in the oxygen poor and contaminated environments in which it is found. Researchers

[1864] https://www.cell.com/consortium/exRNA
[1865] https://commonfund.nih.gov/editing
[1866] Saha K, et al. Nature. 2021 Apr;592(7853):195-204. PMID: 33828315.
[1867] https://commonfund.nih.gov/diseases
[1868] Hoshika S, et al. *Science*. 2019 Feb 22;363(6429):884-887. PMID: 30792304.
[1869] Oran D, et al. *Science*. 2018 Dec 14;362(6420):1281-1285. PMID: 30545883.
[1870] Wang F, et al. *Cell*. 2019 Apr 4;177(2):361-369.e10. PMID: 30951668.

were able to obtain a 3D structure of the nanowires and discovered an appendage never before seen. The bacterium's nanowires, which consist of protein chains with iron molecules at their centers, could have applications in nanotechnologies that require electricity to run.

Facilitating Research

Guiding Collaborative Innovation in Environmental Health

Collaboration and communication across research laboratories and across specific research domains can lead to new innovations and priorities within a field. NIH and the NASEM collaborated to host a series of workshops to discuss several emerging technologies and their impact on and potential uses for environmental health. One workshop explored the current status of single-cell and single-molecule analysis tools and research. Over the course of the workshop, participants reviewed the preliminary use of single-cell and single-molecule analysis tools in environmental health studies and investigated the resources needed to make the data generated most useful to the biomedical and public health fields and to regulatory decision makers. [1871]

In another workshop, participants explored emerging applications and the implications of AI/ML in environmental health research. [1872] Speakers highlighted the use of AI/ML to characterize sources of pollution, predict chemical toxicity, estimate human exposures to contaminants, and identify health outcomes, among other applications. Workshop participants examined how fundamental issues about data availability, quality, bias, and uncertainty in the data used to develop ML algorithms are compounded by lack of transparency and interpretability of AI systems. Participants also discussed how these issues may affect the reproducibility and replicability of results, deliver misleading or inaccurate results, and potentially diminish social trust in research. In a workshop focused on data technology advances, participants explored how advances in the resolution of geospatial technologies can inform efforts in "precision environmental health," which are targeted public health interventions that reach the right populations at the right time. Workshop sessions also focused on the use of geospatial technologies to address environmental justice issues, and on direct responses to environmental disasters.[1873]

NASEM and NIEHS convened the environmental health community to discuss emerging technologies that could help to advance research and decisions on the environmental health effects of microplastics.[1874] Microplastics, or pieces of plastic too small to be seen with the naked eye, are being found throughout the environment. In this workshop, participants explored methods to detect and quantify microplastics in food and the environment, delved into research on the effects of microplastics on the health of humans and wildlife, and discussed ways to reduce microplastics in the environment. These workshops resulted

[1871] https://www.nationalacademies.org/event/03-07-2019/the-promise-of-single-cell-and-single-molecule-analysis-tools-to-advance-environmental-health-research-a-workshop
[1872] https://www.nationalacademies.org/event/06-06-2019/emerging-advances-in-artificial-intelligence-for-environmental-health-research-and-decisions-a-workshop
[1873] https://factor.niehs.nih.gov/2021/5/science-highlights/geospatial
[1874] https://www.nationalacademies.org/our-work/emerging-technologies-to-advance-research-and-decisions-on-the-environmental-health-effects-of-microplastics-a-workshop

in new networks and potential collaborations for tackling these environmental health challenges and in developing innovative technologies to address the challenges.

An initiative that resulted from a previous workshop shows the effect such workshops can have in informing how NIH supports emerging technology. NIEHS and the international environmental health sciences community have created the Environmental Health Language Collaborative, an effort to develop and promote harmonized language in the field.[1875,1876] Through a community model, the collaborative seeks to standardize vocabulary, terminologies, and statistical and modeling approaches, to enhance findability, shareability, and interoperability of data. The group supports increased use of AI/ML to analyze the enormous quantities of data and metadata produced through research. Similarly, the Spatiotemporal Health Analytics Group (SHAG)[1877] seeks to develop spatiotemporal methods and applications in environmental and human health exposure science while also exploring innovative applications of geospatial and spatiotemporal methods in toxicology.

Guiding Collaborative Innovation in Other Fields

NIH has supported another collaborative effort toward developing a behavioral science ontology and a repository of consistent terminology and vocabulary.[1878] This ontology will support rigorous and reproducible behavioral and social science research (BSSR), precision in measurement of mechanisms that drive behavior, and specific targets for behavioral interventions. One such effort included an engagement with the NASEM, along with multiple other sponsors, to complete a consensus study on "Accelerating Behavioral Science Through Ontology Development and Use."[1879] Building on that effort, OBSSR has initiated a project to enhance the integration of up-to-date BSSR terms into NLM's Medical Subject Headings (MeSH) thesaurus, a controlled vocabulary designed to improve discoverability and effective biomedical information retrieval during online searches. NIH has also identified and prioritized terms for addition, sourced standard definitions and synonyms, and proposed additions to the MeSH database. As of a November 2021 update, MeSH now includes 261 additional terms within the domain of attention, learning, and memory, and another 46 for social determinants of health (SDoH). These efforts serve as an important base for future efforts and enhanced engagement in ontology development and use in BSSR.

Technology innovation, like other areas of biomedical and behavioral research, benefits from infrastructure that supports collaboration and communication across research groups. The NIH Research Evaluation and Commercialization Hubs (REACH) program has created a network of eight biomedical proof-of-concept centers, which also includes 48 universities and technical colleges in 12 states to support academic innovators at early stages of product development, helping to convert academic discoveries into

[1875] https://www.niehs.nih.gov/research/programs/ehlc/index.cfm
[1876] Holmgren SD, et al. *Int J Environ Res Public Health*. 2021 Aug 26;18(17):8985. PMID: 34501574.
[1877] https://www.niehs.nih.gov/research/atniehs/labs/bmsb/spatiotemporal/index.cfm
[1878] https://obssr.od.nih.gov/news-and-events/news/director-voice/advancing-ontology-development-and-use-behavioral-and-social
[1879] https://www.nationalacademies.org/our-work/accelerating-social-and-behavioral-science-through-ontology-development-and-use

healthcare solutions.[1880] NIH provides funding and resources to centers and hubs that then provide entrepreneurial training, expert feedback, funding to support early-stage product definition studies, and project management support for funded projects. From the program's inception in 2013 through FY 2021, the projects have led to the creation of 44 startup companies, 21 technology licenses, and $154 million in follow-on investment to continue development of new health care products and services.[1881, 1882, 1883] Despite the relatively lengthy time typically required to commercialize biomedical technologies, several technologies have quickly reached patients in a clinical trial setting or in the consumer marketplace. These include a commercially available artificial brain to improve the power of functional MRI as a diagnostic tool, an online toolkit to address burnout in first responders, which is currently being used by more than 6,500 people in all 50 states, and a new drug that latches onto tumors and prompts the immune system to fight the cancer, which is currently in a phase 1 clinical trial.

Research Resources and Infrastructure

A critical step to fulfilling the NIH mission is to develop, maintain, and renew the scientific human and physical resources that will ensure the nation's capability to prevent and treat disease. The information and ideas that NIH shares with the biomedical research community and the public, along with the advances in computational science and general capacity building, serve as the foundation upon which NIH advances knowledge to improve the lives and health of Americans. Digital tools, physical equipment, workforce training and development, and other initiatives enhance NIH efforts to build research capacity and share knowledge with partners and stakeholders. This section summarizes efforts to develop and utilize research resources and infrastructure that allow NIH to capitalize on its investment in biomedical research.

Summary of NIH Activities

NIH's approach to establishing and maintaining research resources and infrastructure is built on the principle of transparent and equitable information sharing. To ensure that research resources developed with NIH funding are made readily available to the research community for further study, NIH supports a variety of tools and resources. These include knowledge repositories, including databases, gene banks, and digital technologies, to facilitate knowledge and data sharing; collaborations and partnerships that accelerate research; networks and consortia that bring stakeholders together to meet shared goals; infrastructure resources that that enable research; and workshops and other resources that build research capacity.

Knowledge Repositories and Digital Technologies

ClinicalTrials.gov, the world's largest publicly accessible database of privately and publicly funded clinical studies, improves transparency, accountability, and encourages public trust in science. Between FY 2019 and FY 2021, 105,438 studies were registered and 3,416 results summaries were made available on the

[1880] https://seed.nih.gov/programs-for-academics/academic-entrepreneurship-and-product-development-programs/reach
[1881] https://seed.nih.gov/portfolio/stories/LIBH
[1882] https://seed.nih.gov/portfolio/stories/MN-REACH-2
[1883] https://seed.nih.gov/portfolio/stories/MN-REACH

site. During the COVID-19 pandemic, starting in FY 2020 and through FY 2021, some 7,000 newly registered clinical research studies related to COVID-19 were initiated.[1884] In addition, NLM leveraged *ClinicalTrials.gov* to provide comprehensive access to information about nearly 7,000 COVID-19 clinical studies that were included in the WHO's registries.[1885] In FY 2019, NLM launched a major, multi-year modernization of ClinicalTrials.gov to enhance its technical infrastructure, actively engaging with its varied audiences and users and conducting user research.[1886]

Another NLM resource is PubMed®, its database of citations to biomedical literature.[1887] Between FY 2019–2021, NLM added more than 4.4 million citations to PubMed, increasing the total collection to more than 33 million bibliographic citations. PubMed averages more than 3.4 million users each day and more than one billion web searches each year. In FY 2020, NLM launched the updated version of PubMed, featuring a new, responsive design and improved search using "best match" relevance/rank sorting. The best-match function uses a state-of-the-art ML algorithm to help users more easily find highly relevant articles. The new and responsive design is compatible with any screen size, providing the same features and functionality for every device, including tablets and mobile phones. NLM also redesigned a structured PubMed search feature to support user-friendly, efficient searching on clinical and disease-related topics, including COVID-19.

NLM continues to serve as a leader in ensuring free public access to the results of biomedical research through PubMed Central (PMC), its full-text archive of biomedical literature.[1888] NLM added more than 900,000 full-text articles to PMC in FY 2021—expanding this archive to nearly 7.5 million articles. Between FY 2019 and FY 2021, PMC saw a significant increase in users due to the COVID-19 pandemic. In FY 2019, more than 600,000 full-text articles were added to PMC, and there were more than 2.6 million average unique PMC sessions per day. In FY 2020, more than 700,000 articles were added to PMC, with 3.4 million average unique PMC sessions per day. Additionally, NLM enhanced the value of articles deposited in PMC under the NIH Public Access Policy by linking many of them to associated datasets and making available nearly five million articles in machine-readable formats that permit automated analysis through natural language processing.

NLM's Sequence Read Archive (SRA) is the largest publicly available repository for high-throughput genetic sequence data, and as of March 2021 included more than 13 million data records from across the domains of life.[1889] SRA supports a variety of biomedical analyses and discoveries and is freely available to the scientific community and public health researchers. In FY 2020, NLM pioneered the distribution of SRA data to two secure commercial cloud providers, making more than 50 petabytes of data available to researchers and facilitating scalable cloud-hosted computing across the dataset. NLM also launched the

[1884] https://clinicaltrials.gov/ct2/results?cond=COVID-19
[1885] https://governmentciomedia.com/nlm-highlights-essential-role-clinical-databases-pandemic
[1886] https://nlmdirector.nlm.nih.gov/2020/01/07/celebrating-20-years-of-clinicaltrials-gov-and-looking-to-the-future/
[1887] https://pubmed.ncbi.nlm.nih.gov/
[1888] https://www.ncbi.nlm.nih.gov/pmc/
[1889] https://www.ncbi.nlm.nih.gov/sra

COVID-19 Genome Sequence Dataset, which provided free cloud-based access to SARS-CoV-2 SRA data via the NIH STRIDES Initiative.[1890] A subset of SRA is available via a cloud-based open data platform.

Figure 48. Graphic representation of NLM's SRA which is used by more than 100,000 researchers every month. Researchers have a tremendous new opportunity to query this database of high-throughput sequence data in new ways for novel discovery: via the cloud. NLM moved SRA's public data to the cloud, completing the first phase of an ongoing effort to better position these data for large-scale computing. Credit: NLM OCPL

NLM also enhanced research and accelerated the response to the COVID-19 pandemic by improving specialized SARS-CoV-2 virus resources for search and analysis.[1891] NLM partnered with the CDC in the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) consortium to help improve understanding of SARS-CoV-2 transmission, which provided easy and reliable large-scale access to the rapidly growing set of SARS-CoV-2 GenBank® genomes.[1892] NLM's participation in NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Tracking Resistance and Coronavirus Evolution (TRACE) initiative included the development of novel data processes and analysis methodologies to support weekly tracking of the frequency of SARS-CoV-2 sequence mutations and variants, including predictions about variants that may have an impact on therapeutics.[1893]

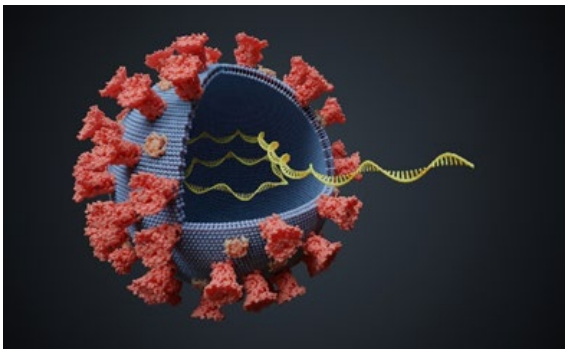


Figure 49. Virus with RNA molecule inside. Viral genetics concept. 3D rendered illustration. Credit: NLM

[1890] https://nlmdirector.nlm.nih.gov/2020/11/04/fostering-a-culture-of-scientific-data-stewardship/
[1891] https://www.ncbi.nlm.nih.gov/labs/virus/vssi/#/virus?SeqType_s=Nucleotide&VirusLineage_ss=taxid:2697049
[1892] https://www.cdc.gov/coronavirus/2019-ncov/variants/spheres.html
[1893] https://www.nih.gov/research-training/medical-research-initiatives/activ/tracking-resistance-coronavirus-evolution-trace

NLM also curates a vast database of completely complete and nearly complete sequenced genomes of bacteria, archaea, eukaroytes, and viruses, which has allowed researchers to establish fundamental principles of genome evolution and to investigate the evolution of biologically and medically important groups of organisms known as phages.[1894,1895] Phages (formally known as bacteriophages) are viruses that solely kill and selectively target bacteria. Analysis of phage genomes identified in whole-community human gut metagenomes resulted in the delineation of at least three new candidate families of *Caudovirales* and revealed diverse putative mechanisms underlying phage–host interactions in the human gut. The addition of these phylogenetically classified, diverse, and distinct phages to public databases will facilitate taxonomic decomposition and functional characterization of human gut viral genomes.

The rapid accumulation of genome sequences and protein structures during the last decade has been enriched by major advances in search methods applicable to sequence databases. NLM is at the forefront of these. NLM researchers contributed to the development and application of advancing methods, such as the powerful Position-Specific Iterating BLAST (PSI-BLAST) method, protein structure comparison methods, homology modeling of protein structure, genome context analysis, custom libraries of protein domain profiles, and computational pipelines for novel domain identification.[1896] These methods for protein motif search are being complemented by deep learning computational methods. Their research on protein domains led to a substantial increase in the repertoire of domains encoded by viruses of prokaryotes and eukaryotes, and to insights into fundamental problems of evolutionary biology including the origin of eukaryotes.

NLM's GenBank is the NIH genetic sequence database. It is the world's largest collection of publicly available annotated nucleotide sequences, containing more than 1.6 billion publicly available nucleotide sequences for 450,000 formally described species.[1897] GenBank provides the biomedical community free and easy access to genome sequences and supports essential open access to sequence data. The database is one of the key tools that scientists use to conduct biomedical and biologic research, and it is designed to provide and encourage access within the scientific community to the most up-to-date and comprehensive DNA sequence information. In FY 2021, NLM streamlined data submission and integrated data validation to support SARS-CoV-2 epidemiology. More than 940,000 total SARS-CoV-2 sequences are available in GenBank (representing some 359,000 complete genomes) and more than 830,000 SARS-CoV-2 sequence read samples are available in Sequence Read Archive (SRA) in FY 2021.

The NIH CDE Repository, developed and maintained by NLM, supports the NIH Strategic Plan for Data Science by streamlining access to CDEs that promote consistency in data collection across NIH-funded research studies.[1898] As part of the effort, NLM created CDE guidance, resources, and training to help the

[1894] Benler S, et al. Microbiome. 2021 Mar 29;9(1):78. PMID: 33781338.
[1895] Yutin N, et al. Nat Commun. 2021 Feb 16;12(1):1044. PMID: 33594055.
[1896] Kvon EZ, et al. Cell. 2020 Mar 19;180(6):1262-1271.e15. PMID: 32169219.
[1897] https://www.ncbi.nlm.nih.gov/genbank/
[1898] https://nlmdirector.nlm.nih.gov/2021/06/23/common-data-elements-increasing-fair-data-sharing/

biomedical and behavioral research communities identify NIH-endorsed CDEs and export CDEs for use in studies; improved use of CDEs by creating a targeted training plan and training course for NIH researchers on CDEs and the CDE repository; advised the NIH-wide CDE Governance Committee and aligned NIH CDE repository functionality with newly established governance policies and procedures; and made the CDE repository more sustainable, and enhanced usability and user experience.

Figure 50. CDEs are a type of health data standard that is commonly used and reused in both clinical and research settings. CDEs capture complex phenomena like depression, or recovery, through standardized, well-defined questions (variables) that are paired with a set of allowable responses (values) that are used in a standardized way across studies or trials. Credit: NLM

NLM researchers are developing and applying novel computational approaches to large clinical databases to study the association between patient characteristics (e.g., age, gender, comorbidities), medication usage, and patient outcomes.[1899] This work provides opportunities to further validate findings from smaller-scale clinical studies and conduct research in areas that lack clinical trials. NLM researchers have succeeded in developing a statistical tool that combines deep learning using AI and statistical methods. The special feature of this tool is that it supports time varying covariates, something that no other tool has been able to do. Specific studies have investigated hormone replacement therapy (HRT), a treatment for menopausal symptoms that may have negative outcomes for women. Studies have also focused on a set of prescription drugs that might reduce or increase incidence and/or severity of COVID-19, and the negative outcomes of proton pump inhibitors, which are used to treat a variety of diseases.

NLM digitizes biomedical resources including journals, books, manuscripts, still images, videos, and maps to preserve their content and to make these resources available through NLM Digital Collections, PubMed Central (PMC), and other repositories. Digitizing the early (or older) literature makes important information available freely and quickly worldwide. This has enormous benefit in understanding responses to previous pandemics, such as the 1918 flu outbreak, as well as in allowing access to the literature without having physical access to a library collection. Between FY 2019–2021, NLM collaborated with partners to digitize more than 33 collections and more than 900 films and videos, in an effort to preserve and enhance access to NLM's unique manuscript and audio and visual collection.

[1899] https://www.nlm.nih.gov/research/focus/Health.html

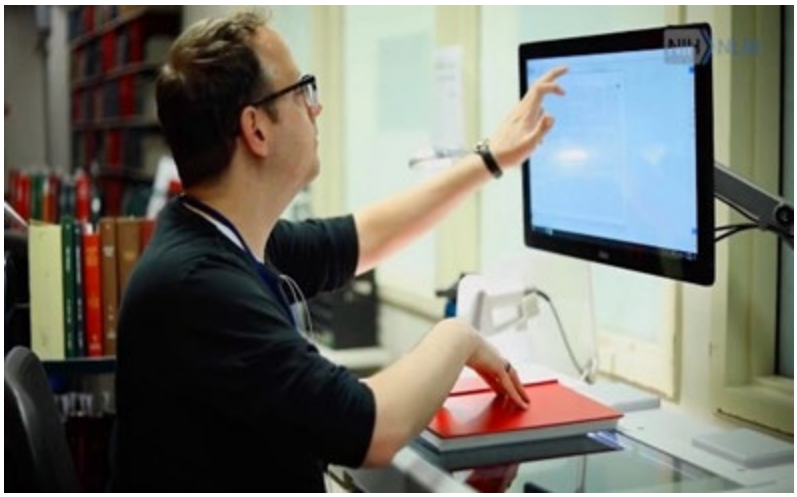


Figure 51. NLM staff digitize books and other literature. Credit: NLM OCPL

The NIH Common Fund's Metabolomics Program aims to catalyze research on the role of metabolomics (the study of chemical reactions that take place in organisms, cells, or tissues) in human health. The program recently began its second phase.[1900] Phase 1 of the Metabolomics program increased national metabolomics research capacity through the establishment of six regional centers and promoted data sharing by establishing a data repository. In its second phase, the metabolomics program developed the National Metabolomics Data Repository, bringing analysis capability to metabolomics data in the repository. The program also generated tools and data for compound identification and metabolomics data analysis and interpretation, and established standards and guidelines for developing metabolomics software and for compound identification and quantification.

The Common Fund's Illuminating the Druggable Genome Program funded the expansion of an "ultra-large virtual docking library" that enables researchers to screen large numbers of molecules to determine which molecules dock with its receptor protein.[1901] By using a computational approach to screening huge numbers of molecules, researchers will need to make and test only the few molecules that match their protein of interest, resulting in a more streamlined process of discovering new targets for medications.[1902]

Further, the NIH Common Fund's Library of Integrated Network-based Cellular Signatures (LINCS) program celebrated its tenth anniversary in 2020,[1903] and major accomplishments of the program were presented at a LINCS Virtual Symposium in November 2020.[1904] LINCS program achievements include creating a catalog of cellular responses (signatures) from various assays (transcriptomics, proteomics, imaging) performed on a variety of different cell types following genetic, small molecule, antibody, or microenvironment perturbations. The LINCS program also generated more than 200 publications, and

[1900] https://commonfund.nih.gov/metabolomics
[1901] https://www.nih.gov/news-events/news-releases/mega-docking-library-poised-speed-drug-discovery
[1902] Lyu J, et al. *Nature* 2019;566(7743):224-229. PMID: 30728502.
[1903] https://commonfund.nih.gov/lincs
[1904] https://commonfund.nih.gov/lincs/virtualsymposium

LINCS assets have been cited in many publications outside of the consortium—a sign of the growing utility of this resource in the study of diverse aspects of human biology.

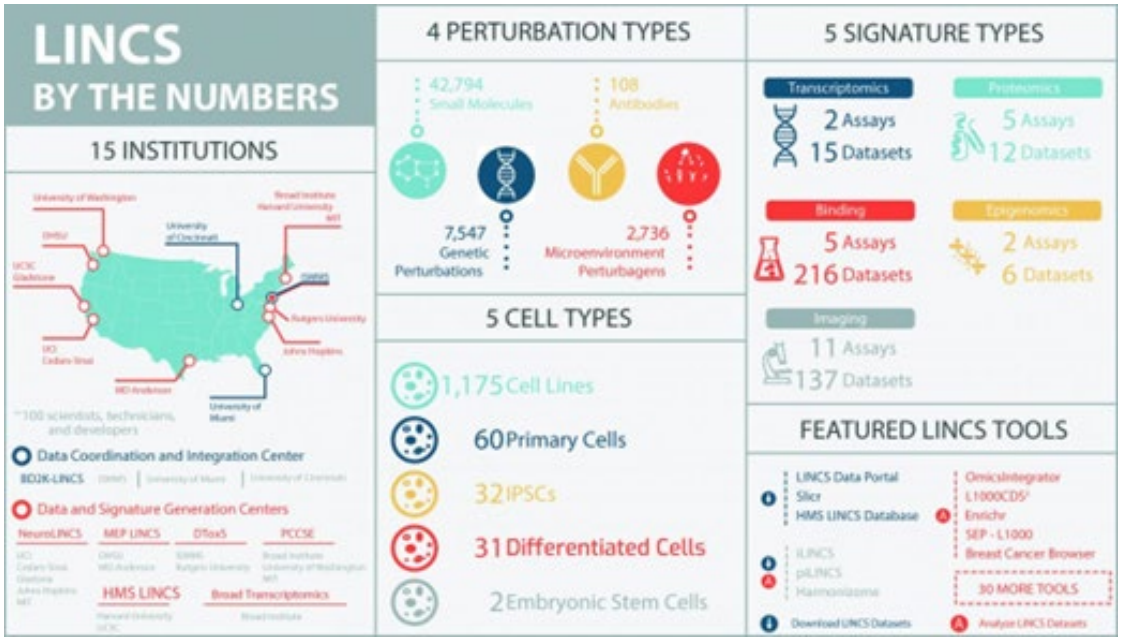


Figure 52. The LINCS program focuses on better understanding human disease by cataloging the changes that occur when cells are exposed to a variety of agents (called perturbagens) that disrupt normal cellular functions. A steadily increasing number of NIH grant applications use LINCS data, and private-sector companies and government organizations have also used LINCS tools and data to develop their approaches for drug discovery and development. Credit: NIH Common Fund

The NIH Common Fund Data Ecosystem (CFDE) aims to enable broad use of NIH Common Fund datasets to accelerate scientific discovery. The CFDE is developing an online discovery portal to enable users to search across NIH Common Fund datasets.[1905] It also supports pilot data analysis projects to engage a broad community of end-users and enable novel cross-cutting biological questions to be formulated and addressed.[1906] CFDE has engaged Data Coordinating Centers from ten different NIH Common Fund programs to help build a functional ecosystem that makes NIH Common Fund data more useful alone and in combination with other datasets.

[1905] https://app.nih-cfde.org
[1906] https://commonfund.nih.gov/dataecosystem

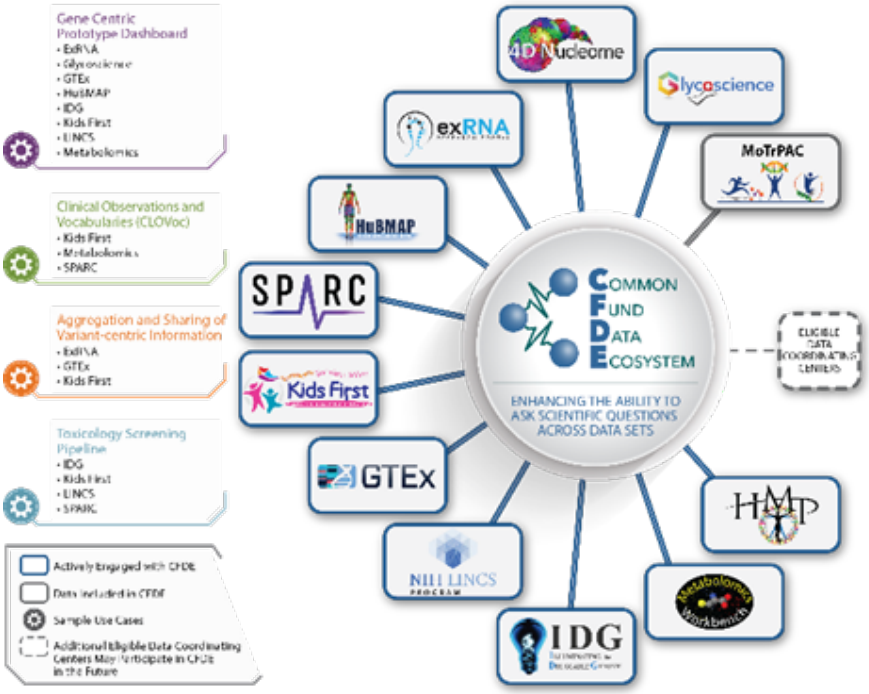


Figure 53. Overview of tools and resources available to researchers within the CFDE portal. Credit: NIH Common Fund

The NIH Pragmatic Trials Collaboratory celebrated ten years of Rethinking Clinical Trials.[1907] Over the past decade, the NIH Pragmatic Trials Collaboratory has supported 22 pragmatic clinical trials spanning 1,100 clinical sites in 45 states and covering a wide range of medical conditions, including kidney disease, fibromyalgia, sickle cell disease, and cardiovascular disease. The program has also produced 232 articles that were published in peer-reviewed journals, 380 presentations and abstracts presented at scientific conferences, and produced more than 400 public Grand Rounds webinars. Best practices and lessons learned about the many facets of study design and conduct are shared publicly on the continually growing online platform known as the Living Textbook of Pragmatic Clinical Trials.[1908] As NIH Common Fund support for this program ends, multiple NIH ICs will continue to support this valuable resource.

[1907] https://rethinkingclinicaltrials.org/news/january-10-2022-nih-collaboratory-celebrates-10-successful-years-of-rethinking-clinical-trials-with-a-new-name-and-a-refreshed-living-textbook/
[1908] rethinkingclinicaltrials.org

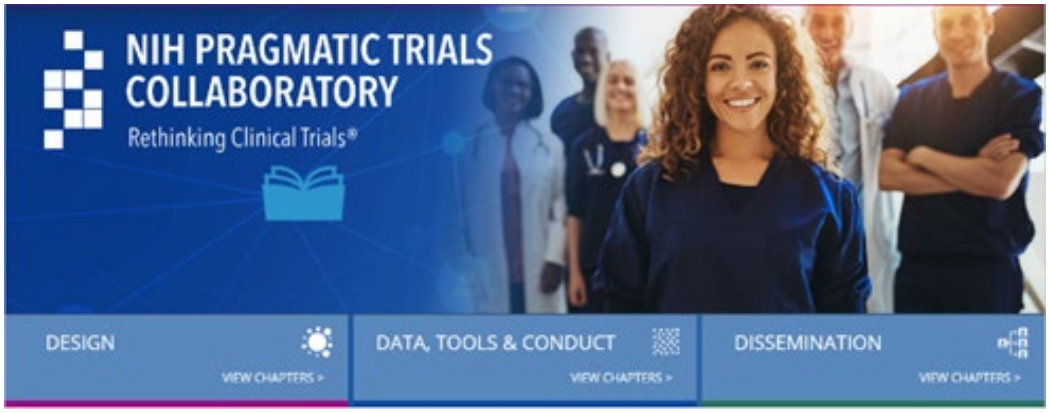


Figure 54. The NIH Pragmatic Trials Collaboratory website offer access to design; data, tools, and conduct; dissemination of valuable research resources. Credit: NIH Common Fund

In May of 2019, *All of Us* Research Program announced the beta release of its interactive data browser, which provided a first look at the data that participants are sharing for health research. Participants, researchers, and other members of the public may use the online tool to learn more about the *All of Us* participant community and explore summary data.[1909] Then in May 2020, the program began beta testing its data platform, the *All of Us* Researcher Workbench, which researchers can use to analyze data in greater detail.[1910] The program adopted a "data passport" model to make the data broadly accessible. After researchers register with the program, agree to its rules, and complete its training on the responsible conduct of research, the program will grant them permission to explore *All of Us* data for a wide range of studies, rather than determining access for all studies on a project-by-project basis. This early version of the Researcher Workbench included data that was generously shared with the program from nearly 225,000 of its first participants, 75 percent of whom are from communities that are historically underrepresented in research, and more than 45 percent represent diverse races and ethnicities. It included information from EHRs; six initial surveys covering demographics, lifestyle factors, and overall health; and baseline physical measurements taken by program staff.

NIH's HEAL Initiative has developed the HEAL Data Ecosystem to accelerate sharing HEAL-generated data and results among the broad community of researchers, healthcare providers, community leaders, policy makers, and other HEAL stakeholders who can benefit from learning the results of initiative research.[1911] The HEAL Data Ecosystem enables the community to search, analyze, and make new discoveries using HEAL data, and it promotes data sharing by empowering researchers to make their HEAL-generated data findable, accessible, interoperable, and reusable. NIH HEAL Initiative data will be accessible via the HEAL Platform, which is a cloud-based environment for finding, accessing, and analyzing data, and which

[1909] https://allofus.nih.gov/news-events/announcements/all-us-research-program-launches-data-browser-offering-preview-landmark-health-database;
[1910] https://allofus.nih.gov/news-events/announcements/all-us-research-program-begins-beta-testing-data-platform
[1911] https://heal.nih.gov/data/heal-data-ecosystem

supports the initiative's mission by maximizing access to and use of NIH HEAL Initiative findings, data, analysis tools, and resources.

NIA supports a variety of longitudinal studies, harmonization projects, archives, and repositories to facilitate research on aging, in the behavioral and social sciences. Recently, NIA established the Health and Aging Data (HaAD) Enclave, a secure cloud-based platform for NIA-funded investigators to conduct faster and easier research analyses using data from NIA-funded studies that are linked to CMS claims.[1912]

The Dietary Supplement Ingredient Database (DSID) provides estimated levels of ingredients in dietary supplement products sold in the U.S.[1913] These statistically predicted estimates may differ from labeled amounts and are based on chemical analysis of nationally representative products. The DSID was developed by the Methods and Application of Food Composition Laboratory, U.S. Department of Agriculture, in collaboration with the ODS and other federal agencies. DSID-4, the fourth release of DSID, reports national estimates of ingredient content in adult, children's, and non-prescription prenatal multivitamin/mineral (MVMs) and omega-3 fatty acid supplements. The DSID is intended primarily for research applications. These data are appropriate for use in population studies of nutrient intake, rather than for assessing content of individual products.

Similarly, the Dietary Supplement Label Database (DSLD), developed by ODS, catalogs all information printed on labels of dietary supplement products sold in the U.S. [1914] The database resulted from specific recommendations to NIH from Congress in 2004 that encouraged the NIH to develop, create, regularly update, maintain, and make available to government and research entities a database of all supplement labels sold in the U.S. The 150,000+ labels in the DSLD are sourced from products reported in national population-based surveys, and through voluntary submissions by dietary supplement manufacturers, and are updated regularly.

Translational efforts rely on data, however, data are often fragmented across different systems and not easily linked. The South Carolina Clinical & Translational Research Institute at the Medical University of South Carolina, part of the NCATS CTSA program, created a digital platform called Research Integrated Network of Systems to facilitate the sharing of study information across multiple CTSA sites.[1915] The virtual data warehouse utilizes a unique research master identifier to both create the linkages between systems and distinguish among individual studies, allowing researchers to effectively run and evaluate outcomes of multi-site studies.[1916]

Repurposing approved drugs to treat a new disease has been a serendipitous affair, subject to chance observations by clinicians. NCATS is systematizing this serendipity through the NCATS Pharmaceutical Collection (NPC), a compilation of 2,900 drugs—nearly every drug approved for human use by major

[1912] https://www.nia.nih.gov/research/blog/2022/02/streamlined-secure-access-cms-study-data
[1913] https://dsid.od.nih.gov/
[1914] https://ods.od.nih.gov/Research/Dietary_Supplement_Label_Database.aspx
[1915] https://www.clinicalresearchnewsonline.com/news/2021/05/10/new-research-data-mart-to-help-academic-sites-track-trial-performance
[1916] He W, et al. *J Am Med Inform Assoc* 2021;28(7):1440-1450. PMID: 33729486.

regulatory agencies worldwide.[1917] NCATS celebrated the NPC's 10th anniversary in 2019. In its first ten years, the NPC had been used in more than 200 projects in such diverse areas as rare diseases, infectious diseases, and cancer. Several projects produced drugs with potential new uses that have since entered clinical trials.

NIH's Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative allows NIH and NIH-funded institutions to begin creating a robust, interconnected data ecosystem that breaks down silos related to generating, analyzing, and sharing research data, while using cloud computing to streamline NIH data use, provided by partnerships with commercial cloud providers.[1918] CloudLab, sponsored by the Office of Data Science Strategy (ODSS), is a program in addition to STRIDES that lowers barriers to accessing cloud environment for NIH researchers. The ODSS High-Value Datasets program supports NIH data science projects as they migrate to cloud computing through the STRIDES initiative.

NIH's Researcher Auth Service (RAS) is a cloud-based authentication and authorization service that facilitates access to the agency's open and controlled data assets and repositories in a consistent, secure, and user-friendly manner.[1919] Researchers use RAS to log in once, and then can work across all RAS-integrated NIH data repositories. This capacity addresses the need to simplify interoperability among these various resources.

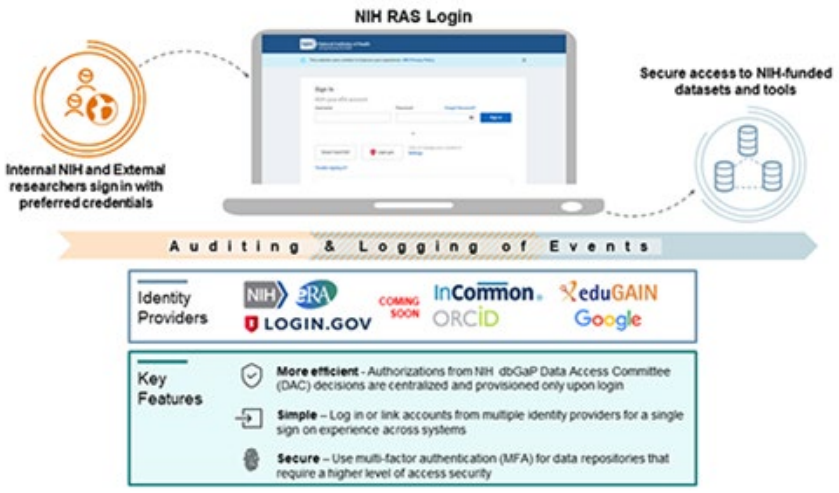


Figure 55. Overview of the RAS authentication and authorization process. Credit: NIH ODSS

NHLBI has been able to build one of the world's largest and most ethnically diverse collections of health-related data from research volunteers, including whole-genome data (a person's complete set of DNA). The Trans-Omics for Precision Medicine (TOPMed) program has amassed nearly four petabytes of de-identified genomic, clinical, imaging, and environmental data from more than 161,000 participants in 80

[1917] Huang, R, et al. *Drug Discov Today* 2019;24(12):2341-2349. PMID: 31585169.
[1918] https://datascience.nih.gov/strides
[1919] https://datascience.nih.gov/researcher-auth-service-initiative

diverse population-based studies, including NHLBI's Framingham Heart Study, Jackson Heart Study, and Hispanic Community Health Study/Study of Latinos.[1920] These data are in a secure cloud-based platform called the BioData Catalyst, which has tools for analyzing large datasets and sharing results in real time. BioData Catalyst provides a virtual collaborative workspace that meets the FAIR threshold for data and access, to all qualified researchers, the vast majority of whom lack their own data science resources.

The NHGRI Clinical Genome (ClinGen) Resource collects phenotypic and clinical information on variants across the genome, develops consensus approaches to identifying their clinical relevance, and disseminates this information to researchers and clinicians.[1921] To date, ClinGen researchers have catalogued more than 10,000 human genomic variants.[1922] In FY 2019, ClinGen's catalog of expert-curated variants became the first public database to be recognized by the FDA as a source of information about those genomic variants that have a high likelihood of resulting in disease. As important, FDA recognition will make it easier to develop and use clinical tests that detect the curated variants in humans.[1923] Looking forward, ClinGen is leveraging working groups that focus on complex disease curation, integrating computational predictors into curation frameworks, and ensuring that ancestrally diverse populations are represented in the resource.

Progress in genomics research and genomic medicine requires that investigators share large datasets and apply complex methods of analysis. The sharing of genomic data, in particular, can be logistically difficult given the ever-increasing size of the datasets and the need to respect the privacy and consent parameters of the research participants. To overcome these challenges, NHGRI created and supports the Genomic Data Science Analysis, Visualization, and Informatics Lab-space (AnVIL) Resource, which provides researchers with a modern, cloud-based environment for storing, sharing, accessing, and analyzing genomic data.[1924] AnVIL was officially opened to the public in FY 2020.

AnVIL already hosts a variety of controlled-access and publicly available datasets, and it is currently the only repository providing access to raw, next-generation DNA-sequencing data from the latest release of the Genotype-Tissue Expression Project.[1925] Other datasets from existing NHGRI-funded clinical research programs, such as the Electronic Medical Records and Genomics Network and the Clinical Sequencing Evidence-Generating Research Consortium, are also being made available on AnVIL. During the COVID-19 pandemic, AnVIL has been used as the genomics data repository for various NIH COVID-19 host genetics studies and for the international COVID-19 Host Genetics Initiative, a consortium studying the genomic determinants of COVID-19 susceptibility, severity, and outcomes.[1926] In addition to a cloud-based infrastructure for data sharing, AnVIL aims to provide pipelines for analyzing genomic data that are tailored for both experienced and novice users. Incorporating simple tools and training modules within a

[1920] https://biodatacatalyst.nhlbi.nih.gov/fellows/cohort1/
[1921] https://www.genome.gov/Funded-Programs-Projects/ClinGen-Clinical-Genome-Resource
[1922] Wilcox E, et al. *J Mol Diagn* 2021;23(11):1500-1505. PMID: 34384894.
[1923] Kanavy DM, et al. *Genome Med* 2019;11(1):77. PMID: 31783775.
[1924] Schatz MC, et al. *Cell Genom* 2022;2(1):100085. PMID: 35199087.
[1925] https://www.genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/Genomic-Analysis-Visualization-Informatics-Lab-space-AnVIL
[1926] Lemieux JE, et al. *Science*. 2021 Feb 5;371(6529):eabe3261. PMID: 33303686.

cloud-based infrastructure will make it possible for AnVIL to engage researchers and communities that have not previously been well-represented in genomics, such as community college and high school students.

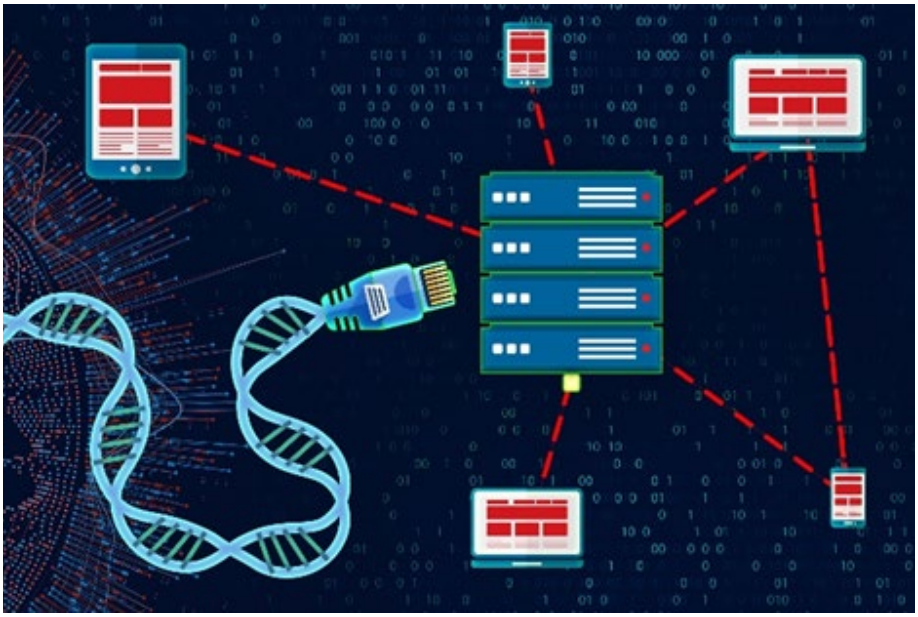


Figure 56. In line with the NIH Strategic Plan for Data Science, AnVIL is working with other ICs to make its platform interoperable with other cloud-based NIH data resources, so that researchers can access and combine datasets and implement analysis workflows from other data resources. Current collaborators include the NCI Genomic Data Commons and NHLBI's BioData Catalyst. Credit: NHGRI

Cell atlases are comprehensive maps of whole organisms that capture the development and morphology of every cell during organismal development and aging. Such atlases are valuable for studying the mechanisms that underly numerous human diseases. ORIP supports two projects, WormGUIDES and WormAtlas, which develop and utilize advanced super-resolution microscope and electron microscope technologies and imaging analysis tools to generate cell atlas in worm *C. elegans* for use by the broad research communities.[1927,1928] Notably, these two projects include improved image acquisition and processing (selective plane illumination microscopy by ~1,000-fold over previous efforts) and newly developed AI approaches for cell tracking in 3D images. These projects have led to discoveries of novel structural and developmental principles of brain development and neuronal circuitry for understanding degenerative diseases and complex behaviors in humans. The projects continue to provide hundreds and thousands of freely accessible high-resolution images that are being viewed by thousands of unique digital visitors.

The Zebrafish International Resource Center (ZIRC) repository supported by ORIP and NICHD offers wild-type and mutant strains of zebrafish representing more than 14,000 unique genes assigned to 45,344 alleles. This resource center is invaluable because zebrafish have been used across the spectrum of

[1927] https://wormguides.org/
[1928] https://www.wormatlas.org/

biomedical research—from cancer and regenerative medicine to schizophrenia and autism. ZIRC also imports and cryopreserves fish lines provided by the research community, preventing duplication of effort and ensuring research rigor and reproducibility. ZIRC is spearheading the optimization of feeding regimes for biomedical fish models through the coordination of three pilot projects involving a multiplatform candidate reference diet test for biomedical fish models.

In order to better understand how biological systems function and to be able to predict how chemicals and other perturbations affect mammalian cells, we need a comprehensive resource of all the known cellular pathways. Scientists at NCATS constructed the BioPlanet, an informatics platform that integrates data from publicly available sources, which have been manually curated and subjected to thorough redundancy and consistency cross-evaluation.[1929] BioPlanet currently annotates nearly 1,700 unique human pathways by source, biological function and process, disease and toxicity relevance, and availability of probing assays. While BioPlanet was initially conceived as a tool to guide systems toxicology efforts, it has implications and applications across the spectrum of systems biology, systems pharmacology, and disease pathophysiology. The BioPlanet browser has been visited nearly 5,000 times in the past year.

In 2020, NIH released a new and modernized Research Portfolio Online Reporting Tools (RePORT) site, as well as a faster and easier-to-use NIH RePORT Expenditures and Results (RePORTER).[1930] The updated RePORT site strives to meet the needs of its users based on feedback received over the years. New features include the addition of a quick-search box, filterable results, new data visualizations, and a new application programming interface that allows users to write computational procedures to retrieve exactly the grants data they need.

Recognized as one of the key emerging technologies underpinning our national competitiveness, AI is helping predict the spread and escalation of a pandemic, speeding up drug and therapeutic discovery, and advancing synthetic biology and other biomedical research and biotechnology development.[1931] Applying recent technology innovation in AI and deep ML, modern high-performance computers successfully predicted how proteins fold, a landmark that represents a huge leap in both the speed of biomedical breakthroughs and the complexity of “in silico” research that can be conducted. ORIP supports high performance computers that power advanced AI and deep learning technologies to enable biomedical research in all areas, from processing huge amounts of -omics data to simulating biological systems, and much more. As an example, the ORIP-funded Big Omics Data Engine 2 supercomputer supports dozens of researchers at some 75 institutions. This enables breakthrough computational research into neuropsychiatric conditions, cancer, and infectious diseases, with data products being shared among the broad scientific community, advancing genetics and population analysis, as well as structural and chemical biology.

[1929] https://tripod.nih.gov/bioplanet/
[1930] https://nexus.od.nih.gov/all/2020/10/13/welcome-the-new-report-and-reporter-tools/
[1931] https://orip.nih.gov/construction-and-instruments/s10-instrumentation-programs

Recognizing that combining ionic and noninvasive imaging modalities allows more comprehensive evaluation of tissue properties and functions, ORIP also funds both ionic and nonionic modes of in vivo imaging systems (IVIS) with advanced features for preclinical biomedical imaging research in animals. A nonionic imaging system, such as MRI, measures molecular responses to alterations of magnetic fields to generate anatomical and functional images of the interior of the body, capturing the structural, functional, and metabolic changes in the physiological processes, such as blood flow, oxygen consumption, brain tractography, and other neuroactivity in resting or active state of the nervous system. As an example, the ORIP-supported IVIS SpectrumCT at a leading research institution is enabling exciting pre-clinical discoveries in cancer, lung injury, obesity, inflammation, and osteoarthritis by combining the broadband wavelengths of bioluminescence and fluorescence imaging with x-ray computed tomography to enable simultaneous anatomical and molecular measurements.[1932,1933,1934] Animals are imaged non-invasively over time to monitor physiological changes or to test new diagnostic agents, allowing the rapid assessment of novel therapeutics, an approach that will certainly translate to humans as precision medicine advances.[1935]

Data collected from in vivo imaging systems, such as the one described above, can be harnessed along with in silico and in vitro data, to understand the toxicity landscape of polycyclic aromatic compounds (PACs). PACs are a structurally diverse class of human-made toxicants found widely in the environment. Unfortunately, information about human exposure and health effects of PACs is limited. To facilitate greater understanding of PAC toxicity in a cost-effective manner, researchers at the NIEHS Division of the National Toxicology Program (DNTP) created an automated approach to identify PAC structures using computer workflows, algorithms, and clusters.[1936,1937] Using existing data on similar compounds, the scientists categorized PACs based on structure and hazard characterization. The analysis results are available and searchable through an interactive web application.

Researchers at NIEHS and the National Toxicology Program developed the Tox21BodyMap to predict which organs in the human body may be affected by a chemical.[1938,1939] The tool will help scientists generate novel hypotheses to test, prioritize chemicals for toxicity testing, and identify knowledge gaps. It combines information about which gene an assay targets, how highly expressed that gene is in a human organ, and at what tested concentrations a chemical generated a positive assay result. The result was an overall picture of chemical bioactivity. The Tox21BodyMap provides multiple visualizations of the data, highlighting target organs on a map of the body, as well as showing a web of network connections and providing downloadable data.

[1932] Cocco E, et al. *Cancer Discov* 2021;11(1):126-141. PMID: 33004339.
[1933] Nagle VL, et al. *Clin Cancer Res* 2021;27(7):1958-1966. PMID: 33495310.
[1934] Cho S, et al. *Mol Cell* 2021;81(10):2064-2075.e8. PMID: 33756105.
[1935] Mani M, et al. *Magn Reson Med*. 2021;86(2):835-851. PMID: 33759240.
[1936] https://factor.niehs.nih.gov/2020/12/papers/dir/index.htm#a1
[1937] Hsieh JH, et al. *Chem Res Toxicol* 2021 Feb;34(2):268-285. PMID: 33063992.
[1938] https://factor.niehs.nih.gov/2020/8/papers/dir/index.htm#a4
[1939] Borrel A, et al. *Nucleic Acids Res* 2020;48(W1):W472-W476. PMID: 32491175.

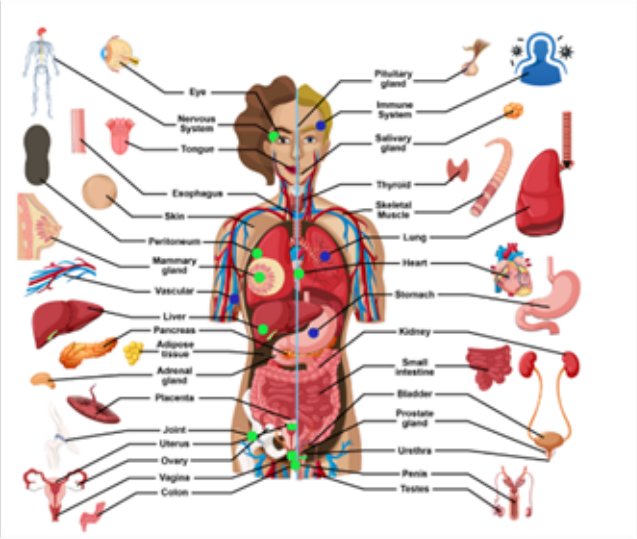


Figure 57. Tox21 BodyMap provides a resource for connecting the effects of environmental chemicals and other agents to specific human organs, systems, and tissues (illustrated in this figure). Credit: NTP

HGBEnviroScreen is another online tool that integrates and visualizes national and local data on environmental health, making data on environmental and social risks more accessible to community members and community-based organizations.[1940] The tool compiles data from five key categories—social vulnerability, baseline health, environmental exposures and risks, environmental sources, and flooding—to create a comprehensive health evaluation. The tool then visualizes the data for each census tract in a pie chart-like graphic known as "ToxPi," while also providing an overall score of community vulnerability.

NIH's Research Methods Resources website provides resources for investigators considering a clinical trial.[1941] Initially, the website focused on group- or cluster-randomized trials and individually randomized group-treatment trials, and both types of trials are common in studies that evaluate behavioral interventions. In 2020, the website was expanded to include materials for stepped wedge group- or cluster-randomized trials, which are widely used for health care delivery interventions. In addition, a new section was added to cover a variety of methods that are broadly applicable in clinical trials supported by NIH, regardless of the nature of the intervention. The website provides resources including background, key references, links to relevant webinars, sample size calculators, and FAQs about the relevant methods.

NLM researchers develop tools and applications that enable researchers to leverage health data standards. One such application is the Fast Healthcare Interoperability Resource (FHIR). [1942,1943] Some of these tools enable standardized data collection using questionnaires and other sources, allowing improved understanding of relationships between data elements.

[1940] https://hgbenviroscreen.org/
[1941] https://researchmethodsresources.nih.gov/
[1942] https://lhcforms.nlm.nih.gov/
[1943] https://nlmdirector.nlm.nih.gov/2019/10/22/addressing-social-determinants-of-health-with-fhir-technology/

NLM researchers advanced the development of computational methods and improved the Viral Annotation DefineR (VADR) software package for viral sequence annotation using models based on NLM's RefSeq annotation.[1944] RefSeq is NLM's open-access, annotated and curated collection of publicly available nucleotide sequences and their protein products. VADR aligns complete input sequences to their nearest RefSeq sequence, and then uses that alignment to map the RefSeq annotation onto the input sequences. It is used by NLM's GenBank to help annotate the protein-coding gene sequences of Norovirus, Dengue virus, and SARS-CoV-2. VADR was improved to allow additional sequences without problems in more essential coding regions (e.g., the spike coding region) to pass VADR and be deposited into GenBank.

NLM researchers also lead the development of automated text-mining techniques to identify various biological entities and concepts (e.g., gene names) in free text, such as the biomedical literature and clinical notes in electronic health records. In particular, they develop state-of-the-art computational technologies for automatically extracting biologically or clinically meaningful relations between those pre-identified entities, such as drug–drug interactions. These researchers investigated computational methods that take advantage of well-constructed ontologies in biomedicine to recognize phenotype information from free text. Specifically, they developed PhenoTagger, which combines both dictionary and ML-based methods to recognize Human Phenotype Ontology concepts in unstructured biomedical text. This achieved competitive performance on the NCBI disease corpus, as compared with state-of-the-art supervised methods, without requiring manually annotated training data. [1945]

The Generalist Repository Ecosystem Initiative works to develop collaborative approaches for data management and sharing by including generalist repositories in the NIH data ecosystem. This better enables search and discovery of NIH-funded data in the generalist repositories.[1946] The main goal is to establish a common set of cohesive and consistent capabilities, services, metrics, and social infrastructure, across generalist repositories. A secondary goal is to raise general awareness and encourage researchers to adopt FAIR principles to better share and reuse data.

Collaborations and Partnerships

NLM is working to bolster its Data Science-Open Science plan with two major collaborations. First, NLM provided leadership and expertise to NIH and other federal agencies to help shape policies and practices for open science. NLM was actively involved in the development of the NIH Statement of Desirable Characteristics for Data Repositories, which was included as supplemental guidance for the implementation of the NIH Data Management and Sharing Plan Policy. These guidelines served as the basis for trans-government guidance that was promulgated by the National Science and Technology Council's Committee on Science's Subcommittee on Open Science (SOS).[1947] NIH is represented by several offices on the SOS, and NLM serves as co-chair of the SOS. As part of these efforts, NLM contributed to development and harmonization of core elements for data management plans across agencies, and by

[1944] Schaffer AA, et al. BMC Bioinformatics. 2020 May 24;21(1):211. PMID: 32448124.
[1945] Luo L, et al. Bioinformatics. 2021 Jan 20;btab019. PMID: 33471061.
[1946] https://datascience.nih.gov/news/nih-office-of-data-science-strategy-announces-new-initiative-to-improve-data-access
[1947] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-016.html

conducting a survey of the persistent unique identifiers in use for digital research objects across U.S. government research agencies. NLM also engaged with external stakeholders including librarians, biomedical researchers, data scientists, data repository experts, standards organizations, and clinicians to advance policies and practices for open science. NLM served as the NIH lead for multiple engagements with the NASEM, which generated open science and data science studies, reports, resources, and workshops on topics including forecasting costs related to biomedical data, safeguarding the bioeconomy (including a strong argument for sharing data internationally to accelerate economic gain), aligning incentives for open science, and research reproducibility and reliability. NLM and NCATS co-sponsored a LitCoin Stakeholder Workshop,[1948] which explored novel modes of scholarly communication including commenting on a particular model for generating micropublications translated to AI-generated triples/assertions and linked with underlying research data.

Next, NLM supported and led activities that explore the ethical implications of open science, and further, developed policies and practices that ensure the ethical implementation of open science.[1949] Ethical considerations include balancing openness of data while protecting participant privacy, reducing propagation of bias in open-source data analysis tools, and addressing access issues to the products of open science. NLM developed a training module on best practices for ethical code sharing and presented it to the participants in NIH Coding it Forward Civic Digital Fellows, the Summer Data Science Fellows, and the NINR Data Science Bootcamp. NLM also established the Science, Technology, and Society Lecture series, which explores the ethical and social implications of biomedical research.

NIH collaborates with other federal agencies to improve public access to the results of federally funded research and to leverage common infrastructure. NIH serves as co-chair of the National Science and Technology Council's SOS. As part of SOS, NIH has led efforts to identify a set of desired characteristics of repositories for the data that results from federally funded research and to identify core elements of data management and sharing plans for adoption across federal agencies. In addition, NLM partnered with the ten federal agencies that now use PubMed Central as a cost-effective support solution for their public-access policies, enabling long-term preservation of and free public access to peer-reviewed journal articles that report on NLM-funded research. NLM also works with other federal agencies that make use of content in PubMed Central to complement their public-access policies and platforms. During the COVID-19 pandemic, many NLM terminologies and health data standards efforts helped support research, public health, and clinical care responses, by rapidly distributing content to address the pandemic. In FY 2020, NLM completed work with FDA and the Office of the National Coordinator for Health Information Technology on a joint project called Developing a Strategically Coordinated Registry Network (CRN) for Women's Health Technologies, which developed and tested a standards-based approach to establishing a CRN that supports data exchange among three separate registries.[1950]

[1948] https://sites.google.com/ncats.nih.gov/litcoin-stakeholder-workshop/home)
[1949] https://nlmdirector.nlm.nih.gov/2021/02/17/nlm-announces-new-annual-lecture-on-science-technology-and-society/
[1950] https://aspe.hhs.gov/sites/default/files/private/pdf/259016/wht-crn-final-reoprt-to-aspe.pdf

ODP also represents NIH as an official liaison on the Community Preventive Services Task Force (CPSTF), which is an independent, nonfederal panel of public health and prevention experts that reviews and assesses scientific evidence to develop recommendations on which community-based health promotion and disease prevention approaches work to improve health.[1951] Recommendations from the CPSTF are published in The Guide to Community Preventive Services and inform decision making about policy, practice, and research priorities for community preventive services. ODP works with the CDC and CPSTF members to provide input into review prioritization and recommendations and to represent the views, concerns, and needs of NIH and its constituents. ODP staff also serve on (or recommend NIH scientists to serve on) systematic review teams where they help disseminate and translate CPSTF recommendations into actions. ODP, through its co-funding program, has provided financial support and subject matter expertise to identify CPSTF priority topics for 2020–2025 and to conduct systematic evidence reviews.

Convened by the Agency for Healthcare Research and Quality (AHRQ), the U.S. Preventive Services Task Force (USPSTF) is an independent, nonfederal panel of recognized experts in disease prevention, evidence-based medicine, and primary care.[1952] The USPSTF reviews, assesses, and evaluates scientific evidence relating to a broad range of clinical preventive health care services. This includes screening, counseling, and preventive medications, and the development recommendations for primary care clinicians and health systems that are published in the form of USPSTF's Recommendation Statements. ODP works closely with AHRQ and the USPSTF to provide scientific input from NIH ICOs on draft research plans, draft evidence reviews, and draft recommendations for clinical preventive services. ODP also disseminates information to NIH ICOs about high-priority evidence gaps for clinical preventive services that have been identified by the USPSTF. In 2021, ODP published a manuscript on the characteristics of evidence that informed changes to USPSTF recommendations.[1953] During 2019–2021, the USPSTF closely reviewed its processes, methods, and recommendations with a commitment to eliminating health disparities. The USPSTF published several manuscripts on the topics of systemic racism, social risk, and health equity.

ODS created the Federal Working Group on Dietary Supplements (FWGoDS) to facilitate communication with representatives from federal agencies that share information and discuss issues, initiatives, and research related to dietary supplements.[1954] FWGoDS was established, in part, on the basis of a Congressional law that specifies that ODS serve as an advisor to federal health agencies on issues related to dietary supplements. It also exists in response to a goal in the ODS Strategic Plan to expand and conduct outreach efforts that inform and educate about supplements. The mission of the FWGoDS is to strengthen collaborative efforts involving dietary supplement education and related communications across the government. ODS also created the NIH Dietary Supplement Research Coordinating Committee (DSRCC) in 2022 to increase collaboration among NIH ICOs that are involved with dietary supplement research.[1955] The DSRCC will facilitate the development of workshops, training, resources, FOAs, or other activities to

[1951] https://www.thecommunityguide.org/
[1952] https://www.uspreventiveservicestaskforce.org/
[1953] Klabunde N, et al. Am J Prev Med. 2022 Feb;62(2):e77-e86. PMID: 34657771.
[1954] https://ods.od.nih.gov/About/federalworkinggroupondietarysupplements.aspx
[1955] https://ods.od.nih.gov/About/NIHDSRCC.aspx

disseminate information on dietary supplement research efforts and stimulate new research. It will also provide input to the ODS director on the scientific gaps in dietary supplement research, mechanisms to promote collaborative initiatives across NIH and within the federal government, and programmatic and policy issues and activities that affect ODS or to which ODS can contribute.

NIH also facilitates strategic alliances between NIH-funded innovators and private sector stakeholders by providing registration, event preparation, and "pitch" coaching to more than 100 Small Business Program awardees per year.[1956] Small businesses are matched to relevant events by technology type, stage of development, and size and type of investment sought. NIH Entrepreneurs in Residence assist businesses in preparing compelling pitches and help identify investors and partners. Furthermore, NIH's company showcase support activities also help increase awareness of NIH to non-traditional constituencies, including angel investors, venture capitalists, technology transfer organizations, and state economic development agencies.

NCATS has entered into a research collaboration agreement with BurstIQ, a provider of block-chain-based exchange solutions to address the protection of intellectual property associated with NCATS' work on translational science.[1957] The NCATS computational infrastructure will integrate BurstIQ's blockchain platform to manage and share intellectual property-sensitive data across the NCATS network.

As the pace of genomic and genetic research increases, the development of research teams that have the expertise and flexibility to respond rapidly to the large number of emerging and evolving ethical, legal, and social implications (ELSI) issues is critical.[1958] The Centers of Excellence in ELSI Research (CEERs) bring together investigators from multiple disciplines to work in innovative ways. Together they address important new—or particularly persistent—ethical, legal, and social issues related to advances in genomics. In addition, the CEERs will support the growth of the next generation of researchers on the ELSI issues of genomic research. The CEER program currently supports five research centers at universities across the country. One of these centers studies the privacy risks associated with genomic information, the effectiveness of legal and policy efforts to reduce privacy risks, and the likelihood that lapses in protecting genomic information will allow people to be identified. To provide a platform for the coordination and synthesis of ELSI research and research products, NHGRI established the Center for ELSI Resources and Analysis in 2019.

[1956] https://seed.nih.gov/support-for-small-businesses/commercialization-enhancement-programs/entrepreneurial-development#partnership
[1957] https://burstiq.com/burstiq-and-the-national-center-for-advancing-translational-sciences-ncats-at-the-national-institutes-of-health-nih-collaborate-to-apply-blockchain-to-intellectual-property-management/
[1958] https://www.genome.gov/Funded-Programs-Projects/ELSI-Research-Program/Centers-of-Excellence

Figure 58. Centers of Excellence in ELSI Research at NHGRI ensure genomic research and associated date collected for research are being used ethically and responsibly. Credit: NHGRI

Due to the complexity of accessing CDC's National Death Index (NDI) data, NIH decided to explore ways to help both intramural and extramural researchers access the NDI more easily.[1959] Led by OBSSR, NIH entered into an agreement with CDC, and as of January 2020, NIH-supported investigators will be able to link their research data more easily to the NDI.

Networks and Consortia

NHGRI has funded Centers of Excellence in Genome Sciences (CEGS), which are designed to provide transformative advances in genomics.[1960,1961,1962] Each CEGS engages an interdisciplinary team of researchers that develops highly innovative genomic approaches to address important biological and biomedical research problems. CEGS also include an education and outreach component that leverages the strengths of the CEGS consortium and its investigators to add value to the genomics capabilities of the host institution and region. To further develop this scientific infrastructure, in FY 2020 and FY 2021, Congress allocated $10 million and $12.5 million, respectively, to fund CEGS at institutions that have not previously received a CEGS award. To date, 15 CEGS have completed their funding after five to ten years of support, while ten CEGS have ongoing funding.

[1959] https://irp.nih.gov/catalyst/v28i6/news-you-can-use-national-death-index#:~:text=The%20NDI%20assists%20investigators%20in,%2C%20and%20death%2Dcertificate%20numbers.https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-057.html

[1960] https://www.genome.gov/Funded-Programs-Projects/Centers-of-Excellence-in-Genomic-Science

[1961] Woronik A, et al. *bioRxiv* 2020:2020.07.30.228890. PMID: 32766578.

[1962] Elisseeff J, et al. *N Engl J Med*. 2021;385(26):2451-2462. PMID: 34936741.

The Encyclopedia of DNA Elements (ENCODE) is a public research consortium managed by NHGRI aimed at identifying all functional elements in the human and mouse genomes to understand their roles in biological processes and human disease.[1963] The fourth phase, ENCODE 4, has created a more comprehensive catalog of candidate functional elements across the human genome and developed a better understanding of those elements through characterization studies, computational analyses, and data integration, through its support of specialized Characterization Centers. Today, ENCODE provides an invaluable catalog containing information about many thousands of functional elements in the human genome. That catalog is now routinely used by researchers from all areas of biomedical sciences, and more than 3,100 scientific publications have reported the use of ENCODE data in their studies.

Clinical Sequencing Evidence-Generating Research (CSER2) is a national, multisite, interdisciplinary research program that seeks to study the effectiveness of integrating genome sequencing into the clinical care of diverse and medically underserved individuals.[1964] CSER2's research goals include measuring the clinical utility of sequencing through patient and familial responses to genomic testing, and by evaluating patient–provider–laboratory interactions that influence the use of sequencing. At least 60 percent of CSER2 research participants are recruited from undeserved and underrepresented groups and healthcare systems. Beginning in August 2017, NHGRI, NCI, and NIMHD jointly funded a second phase of the CSER2 program, which culminated in FY 2021 and resulted in hundreds of applications. For example, the CSER2 Consortium recently published work on incorporating stakeholder feedback into study design in an effort to reduce health disparities and, in conjunction with ClinGen, to standardize the collection of race, ethnicity, and ancestry data.[1965] Moving forward, CSER2 will foster new partnerships with other NHGRI consortia and NIH's *All of Us* Research Program to identify new research and learning opportunities.

The primary goal of the Electronic Medical Records and Genomics (eMERGE) Network is to develop, disseminate, and apply approaches to research that combine biorepositories with electronic medical record (EMR) systems for genomic discovery and genomic medicine implementation research.[1966,1967] The consortium also includes a focus on social and ethical issues such as privacy, confidentiality, and interactions with the broader community. eMERGE concluded its third phase in May 2019, during which it studied candidate pharmacogenomics-relevant genes in thousands of participants and examined barriers to implementing pharmacogenomic approaches in medical care. In its fourth and current phase, eMERGE is investigating how best to incorporate new and more complex data, such as polygenic risk scores, into a patient's EMR. In July 2020, NHGRI committed $75 million in funding over five years for the eMERGE Genomic Risk Assessment and Management Network, which will establish protocols and methodologies for improved genomic risk assessments for diverse populations and integrate the use of those protocols into clinical care.

[1963] https://www.genome.gov/Funded-Programs-Projects/ENCODE-Project-ENCyclopedia-Of-DNA-Elements
[1964] https://www.genome.gov/Funded-Programs-Projects/Clinical-Sequencing-Evidence-Generating-Research-CSER2
[1965] https://cser-consortium.org/
[1966] https://www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE
[1967] https://emerge-network.org/

Since the origin of the human reference in the completion of the International Human Genome Project, there has been a need to maintain and improve the human reference and to make it available to the community.[1968] In March 2018, NHGRI convened an online meeting of more than 65 basic research, clinical, and bioinformatic scientists to discuss scientific opportunities for the genome reference. The meeting addressed key research and resource opportunities for improving the human reference, activities necessary to keep the reference relevant and useful, clinical and research community needs (including education), related resources, and collaborations. The high-level conclusion of the meeting was that the current version of the human reference does not adequately represent human haplotype variation, that the existing tools to include alternative haplotype information in analyses are not well-used, and that there is an opportunity to significantly improve the human reference by developing it into a "pangenome." As a result, NHGRI created a multi-component Human Genome Reference Program in FY 2019 intended to enable an improved "pangenome" reference for the community, and to foster its long-term sustainability and improvement.[1969]

The Telomere-to-Telomere (T2T) Consortium, which aims to generate the first complete assembly of the human genome, is partially funded by NHGRI and will fill in the gaps in our understanding of the human genome sequence, laying a foundation for future research efforts in genomic medicine.[1970] The recent generation of a complete sequence of the human X chromosome represents the start of a new era in which truly comprehensive views of genomes will be acquired.

[1968] https://humanpangenome.org/
[1969] https://www.genome.gov/Funded-Programs-Projects/Human-Genome-Reference-Program
[1970] https://www.genome.gov/about-genomics/telomere-to-telomere

Figure 59. Overview of the Human Genome Project provides insight into gaps T2T Consortium will fill. Credit: NHGRI

To facilitate better use of genomic data, NHGRI and NCI are partnering to fund grants to establish and support the Polygenic Risk MEthods in Diverse populations (PRIMED) Consortium. By studying much larger numbers of non-European individuals, PRIMED will work to improve methods by which people can learn about their genetic risk for developing a disease, with the long-term aim of improving genomic-based prediction methods in all populations.[1971] The PRIMED Consortium includes eight study sites, each of which will take a unique approach to improving PRS development and collaborate using 120 datasets from

[1971] https://www.genome.gov/Funded-Programs-Projects/PRIMED-Consortium

more than 40 different countries. The overall goal of the program is to collectively develop methods that are widely available to the biomedical research community and to build a robust foundation for the large-scale use of PRSs in clinical practice.

NHGRI's Implementing Genomic in Practice (IGNITE) Network was established in 2013. Building on the successful genomic medicine projects of IGNITE I, the second phase of IGNITE began in 2018.[1972] The Pragmatic Clinical Trials Network comprises five multi-site Clinical Groups and one Coordinating Center involving diverse settings and populations, to conduct pragmatic clinical trials of genomic medicine interventions. One trial will study the use of pharmacogenomics in treating post-surgical pain, chronic pain, and depression. The second trial studies the effects of returning genomic risk information to hypertensive patients of African ancestry and their primary care providers to better understand renal disease disparities across the U.S. These trials will allow the assessment of both clinical utility and cost-effectiveness of genomic medicine interventions in diverse clinical settings.[1973,1974]

Led by FIC, NLM, NIMH, and NIBIB, the NIH Common Fund's Harnessing Data Science for Health Discovery and Innovation in Africa program is supported by the OD and 11 ICOs. This program aims to leverage data science technologies and prior NIH investments to develop solutions to Africa's most pressing public health problems through a robust ecosystem of new partners from academic, government, and private sectors. The program is in the process of establishing a consortium consisting of a data science platform and coordinating center, seven research hubs, seven data science research training programs, and four projects focused on studying the ELSI of data science research. Awardees are building a robust network of partnerships across the African continent and in the U.S., including numerous national health ministries, nongovernmental organizations, corporations, and academic institutions.

The Collaborative Centers in Children's Environmental Health Research and Translation program aims to establish a national network of centers to develop strategies to translate key children's environmental health research findings to relevant stakeholders.[1975] Awards for six centers and a coordinating center were made in FY 2021.

NIGMS is among the largest sponsors of infectious disease research at NIH. As part of these research efforts, NIGMS supports the Models of Infectious Disease Agents Study (MIDAS), a collaboration among scientists who conduct research in mathematical and computational modeling to improve the detection, mitigation, and prevention of emerging infectious disease threats. The MIDAS Coordination Center plays a key role in organizing and facilitating infectious disease modeling research by coordinating communications among researchers, students, public health agencies, practitioners, and officials. The Center also provides specific data services, such as access to curated data sets, models, algorithms, code, parameters, and cloud computing capabilities. In addition, the Center has established an online portal for

[1972] https://www.genome.gov/Funded-Programs-Projects/Implementing-Genomics-in-Practice-IGNITE-Pragmatic-Clinical-Trials-Network
[1973] https://gmkb.org/
[1974] https://gmkb.org/publications/
[1975] https://www.niehs.nih.gov/research/supported/centers/collaborative/index.cfm

COVID-19 modeling research, which provides an extraordinary collection of data and information regarding the coronavirus pandemic.[1976]

In 2020, the Genotype-Tissue Expression (GTEx) Consortium published its final set of studies analyzing genotype data from approximately 948 post-mortem donors and approximately 17,382 RNA-seq samples across 54 tissue sites and two cell lines, with adequate power to detect Expression Quantitative Trait Loci in 48 tissues.[1977] NHGRI and NICHD collaborated on a new initiative called developmental Genotype-Tissue Expression (dGTEx). The primary goal of dGTEx is to establish a resource database and associated tissue bank to study gene expression patterns in multiple relatively healthy reference neonatal, pediatric, and adolescent tissues, and to make this resource broadly available for further research. The dGTEx resource will be a powerful tool, providing a comprehensive dataset of gene expression across a wide range of human tissues throughout development, filling an extant gap in genomic databases across developmental stages. To complement dGTEx, NHGRI recently launched the Non-Human Primate Developmental Genotype-Tissue Expression project (NHP dGTEx), a set of parallel NHP tissue collections for comparative genomic assessment of tissue-specific gene expression at distinct developmental stages.

Policies, Programs and Resources that Enable Biomedical Research

The NIH Inclusion Across the Lifespan (IAL) policy, implemented in response to the *21st Century Cures Act*, requires that individuals of all ages (including children and older adults) be included in our supported clinical research, absent compelling scientific or ethical reasons not to include them.[1978] Recipients whose projects fall under the policy have been submitting anonymized individual-level data on the sex, gender, race, ethnicity, and age of their participants when they enroll, as part of their progress reports. The Research Inclusion Statistics Report now has a table with FY 2021 data on participant age at enrollment, broken down by NIH Research, Condition, and Disease Classification (RCDC) category.

Sharing scientific data is fundamental to accelerating biomedical research discovery. In order to enable researchers, clinicians, students, and the public, to access research results from NIH-funded projects and to expedite the translation of research results into improvements in human health, NIH published a draft Policy for Data Management and Sharing in 2019 for public comment, after several iterations of public engagements.[1979] Guided by public comments, Tribal consultation, recommendations from the Secretary's Advisory Committee for Human Research Protections, and input from the SOS, NIH revised the draft policy and the published the final NIH Policy for Data Management and Sharing on October 29, 2020.[1980] The policy directs that, for all NIH-supported research, a Data Management and Sharing Plan will be developed that maximizes appropriate sharing of scientific data. Through this policy, NIH hopes to change the culture of research to make planning for data management and sharing a routine part of research, thereby increasing the rigor, reproducibility, and transparency of NIH-funded research. To allow sufficient time for the research community to prepare for implementation of this policy, an effective date of January 25,

[1976] https://midasnetwork.us/covid-19/
[1977] https://www.genome.gov/Funded-Programs-Projects/Developmental-Genotype-Tissue-Expression
[1978] https://nexus.od.nih.gov/all/2022/04/11/fy-2021-data-on-age-at-enrollment-in-clinical-research-now-available-by-rcdc-category/
[1979] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-013.html
[1980] https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html

2023, has been set. NIH has provided numerous resources to guide implementation and will continue to do so as the policy becomes standard.[1981]

As cannabis becomes more available and more socially accepted in the U.S., it is increasingly important to facilitate research on the drug's effects. A major hindrance, however, has been the lack of a standard unit by which to measure cannabis intake, which would allow researchers to compare its effects across studies. Existing experimental data are often hard to interpret due to wide variability in potency of cannabis plant material and extracts, the lack of standard measures of use, and the numerous ways people consume cannabis. To help rectify this, NIDA, along with NCI, NHLBI, and NIMH, published a notice in the NIH Guide directing researchers to measure and report their findings from clinical research on cannabis using a standard unit of delta-9-tetrahydrocannabinol of five milligrams.[1982,1983] Adoption of a standard unit for measuring and reporting purposes will facilitate data interpretation and will make it possible to design experiments on drug effects that have real-world relevance, and it will make it easier to translate that research into policy and clinical practice.

Glycans are large carbohydrates that play many roles in the proper functioning of cells. However, studying glycans is challenging, in part because it is difficult to obtain quantities of glycans from nature that are large enough for research purposes. Furthermore, synthesizing glycans is time consuming and labor intensive, in some cases requiring more than 100 steps in specialized laboratories. Researchers supported by the NIH Common Fund's Glycoscience Program developed new approaches to synthesizing glycans, including one approach that involves ten or fewer steps, which expands the availability of glycans for biomedical research.[1984]

Modern cryo-electron microscopy (cryo-EM) instruments allow scientists to observe and understand how biological molecules function and interact, without damage to the organic molecule structure, compared with conventional electron microscopy. This information contributes to a deeper understanding of disease processes at unprecedented optical resolutions, thereby accelerating development of therapeutic interventions. For example, using such instruments combined with AI, ORIP-funded researchers have generated a 3D image of the SARS CoV-2 Nsp2 protein (an important player in the virus's manipulation of the immune system), paving the way to identify potentially life-saving treatments. Contributing to NIH-wide initiatives, ORIP's shared instrumentation program enabled researchers to equip core facilities with cryo-EM instruments for studying the complex molecular and cellular structures of pathogens, cells, and biologically important proteins.[1985]

In June 2019, NIGMS posted the Limited Competition: NIGMS National and Regional Resources award. These awards are intended to ensure that key NIGMS-supported resources remain up-to-date and readily accessible to researchers. As of FY 2021, NIGMS made 12 awards, supporting resources such as materials

[1981] https://sharing.nih.gov/
[1982] https://nida.nih.gov/about-nida/noras-blog/2021/05/establishing-5mg-thc-standard-unit-research, https://grants.nih.gov/grants/guide/notice-files/NOT-DA-21-049.html
[1983] https://grants.nih.gov/grants/guide/notice-files/NOT-DA-21-049.html
[1984] https://commonfund.nih.gov/glycoscience/highlights
[1985] https://orip.nih.gov/about-orip/research-highlights/cryo-electron-microscopy-used-bridge-micro-nano-gap-0

and organism repositories, computational modeling services, imaging and spectrometry centers, and software.[1986]

ODP systematically monitors NIH investments in applied prevention research. In collaboration with the NIH Office of Portfolio Analysis, ODP annually identifies specific research projects that focus on primary and secondary prevention in humans and on applied prevention-related methods.[1987] Using a comprehensive taxonomy and protocol, ODP further characterizes these prevention research projects by rationale, exposure, outcome, population focus, study design, and prevention research type. Publication topics include mortality and disability prevention, diet and physical activity research, substance use prevention, and primary and secondary prevention research.[1988,1989,1990,1991]

iCite is a tool that was developed by the NIH Office of Portfolio Analysis to access a dashboard of bibliometrics for papers associated with a portfolio.[1992] Users are able to issue a query in PubMed or upload the PubMed IDs of articles of interest. iCite has three modules: Influence, Translation, and Open Citations. *iCite: Influence* provides Relative Citation Ratio values, which measure the scientific influence of each paper by field- and time-adjusting the citations it has received, and benchmarking to the median for NIH publications, the value of which is set at 1.0.[1993] *iCite: Translation* measures the degree to which each paper is oriented to human, animal, or molecular/cellular biology, and then uses this information to track and predict citation by clinical articles.[1994] *iCite: Citations* disseminates link-level, public-domain citation data from the NIH Open Citation Collection.[1995]

A team of researchers at NCATS and the NIH Common Fund Regenerative Medicine Program's Stem Cell Translation Laboratory (SCTL) tested more than 15,000 FDA-approved drugs and compounds that led to identification of small-molecule cocktails that would protect induced Pluripotent Stem Cells (iPSCs) from cellular stress and improve cell survival.[1996] They found a four-factor drug combination, made up of chroman 1, emricasan, polyamines, and trans-ISRIB (CEPT), which preserves cell survival through processes that include protection from DNA damage and lowering of oxidative stress.[1997] Additionally, the team demonstrated that treating iPSCs with CEPT makes establishing new types of iPSCs more feasible and production of larger quantities possible. Thus, the CEPT cocktail has the potential to support scaling up of iPSCs for clinical use.[1998] The SCTL is also a part of the NCATS Intramural Research Program.

[1986] https://www.nigms.nih.gov/Research/mechanisms/Pages/NIGMS-National-and-Regional-Resources-(R24).aspx
[1987] https://prevention.nih.gov/funding/portfolio-analysis-nih-prevention-research
[1988] Vargas AJ, et al. *JAMA Netw Open* 2019;2(11):e1914718. PMID: 31702797.
[1989] Vargas AJ, et al. *Am J Prev Med* 2019;57(6):818-825. PMID: 31753263.
[1990] Villani J, et al. *Drug Alcohol Depend* 2020;206:107724. PMID: 31753731.
[1991] Murray DM, et al. *Am J Prev Med* 2021;60(6):e261-e268. PMID: 33745818.
[1992] https://icite.od.nih.gov/
[1993] Hutchins BI, et al. *PLoS Biol* 2016;14(9):e1002541. PMID: 27599104.
[1994] Hutchins BI, et al. *PLoS Biol* 2019;17(10):e3000416. PMID: 31600189.
[1995] Hutchins BI, et al. *PLoS Biol* 2019;17(10):e3000385. PMID: 31600197.
[1996] https://commonfund.nih.gov/stemcells
[1997] Chen Y, et al. *Nat Methods* 2021;18(5):528-541. PMID: 33941937.
[1998] https://ncats.nih.gov/news/releases/2021/scientists-identify-small-molecule-cocktail-to-improve-stem-cell-use-in-research-and-disease-treatments

To capture important differences in genetic variability, GTEx researchers analyzed messenger RNA sequences within thousands of healthy tissue samples collected from people who died of causes other than cancer. Those analyses showed that most people (95 percent) had one or more tissues with pockets of cells carrying new genetic mutations.[1999, 2000] The findings clearly show that, even within normal tissues, the DNA in the cells of our bodies is not perfectly identical.

ORIP also supports three Centers for Precision Disease Modeling. At these centers, researchers evaluate the likelihood of a particular human genetic variant to cause disease in optimized model organisms and integrate their findings into clinical care and clinical trials. These centers have developed techniques for robust phenotyping to determine whether specific genetic changes recapitulate a human phenotype. They have also created and validated numerous animal models in different fruit flies and mice, conducted a wide range of studies that increase the understanding of how gene mutations influence cellular and organismal phenotypes, and supported large numbers of preclinical studies using assisted precision-directed therapies.[2001, 2002, 2003] Overall, the three centers have published more than 100 research articles and have collaborated on numerous projects across the nation. One publication laid the groundwork for a phase 1 clinical trial by improving understanding of an inhibitor of the *KRAS* gene, a cancer-causing gene known to be activated in one-third of cancers.[2004]

Animal Models

NLM launched development and implementation of the NIH Comparative Genomics Resource (CGR) in FY 2021 to maximize the impact of eukaryotic research organisms and their associated genomic data resources on biological and medical research.[2005] This 5-year, NIH-funded initiative aims to establish an ecosystem for reliable comparative genomics analyses for all eukaryotic organisms, creating a centralized suite of repositories and knowledgebases that offer high-value, integrated, and cloud-ready genome-associated data, tools, and interfaces that are compatible with community-provided organism resources. The effort will be extensively informed by and aligned with the research community throughout its development. Communities at large will be able to use the CGR framework and interfaces to create additional tools that can be focused on specific research questions or organisms, exercise novel or creative approaches, or enable specific technologies. At its completion, CGR will make sophisticated tools and resources for genomes and genome products available for all eukaryotic organisms, provide natural navigation of data within and among different organisms, provide an essential framework on which commercial or grant-funded tools can be developed or datasets connected, and provide a genomics-related data corpus amenable to new computational approaches, such as AI/ML.

[1999] https://directorsblog.nih.gov/2019/06/18/study-finds-genetic-mutations-in-healthy-human-tissues/
[2000] Yizhak K, et al. *Science* 2019;364(6444):eaaw0726. PMID: 31171663.
[2001] https://orip.nih.gov/about-orip/research-highlights/drug-discovery-platform-rapidly-diagnose-patients
[2002] https://www.genomeweb.com/cancer/fruit-fly-model-provides-personalized-cancer-therapy-recommendation#.YSVi6YhKg_U
[2003] https://www.genomeweb.com/cancer/startup-my-personal-therapeutics-apply-ai-fruit-fly-models-cancer-rx-recommendations#.YSVjCYhKg_U
[2004] Bangi E, et al. *Sci Adv* 2019;5(5):eaav6528. PMID: 31131321.
[2005] https://nlmdirector.nlm.nih.gov/2021/02/03/a-journey-to-spur-innovation-and-discovery/

Figure 60. This image represents the CGR Initiative which will improve the data foundational to analyses that rely on comparisons of diverse genomes in NLM databases, increase its connectivity to related content, and facilitate the discovery and retrieval of this information. Just as researchers look to the data from these organisms to teach them about a wide range of fundamental biological processes underpinning human health, NLM relies on the research community to help inform the development and delivery of organism-agnostic core tools and interfaces for CGR so that it can best support these analyses. This initiative will improve the data foundational to analyses that rely on comparisons of diverse genomes in NLM databases, increase its connectivity to related content, and facilitate the discovery and retrieval of this information. Credit: NLM OCPL

Although organ transplants from other species could address the shortage of human organs for transplantation, major obstacles to successful xenotransplantation include organ rejection and the potential for cross-species infection by new infectious agents. To overcome these challenges, the National Swine Resource and Research Center (NSRRC) has been engaged with the research community and other NIH ICO partners to meet the need for xenotransplantation resource infrastructure. Researchers are exploring a variety of strategies to create pig models that can prevent or minimize both rejection and cross-species infection.[2006] NSRRC also provides invaluable services to the research community by creating, upon request, new genetically engineered swine models, such as the phenylketonuria model and the cardiovascular development and congenital heart disease models. Additional models in the pipeline include Alzheimer's disease, variants for xenotransplantation, asthma, Fanconi Anemia, pulmonary fibrosis, Hermansky-Pudlak syndrome, type II diabetes, retinitis pigmentosa, Usher Syndrome Type 2A, and cardiovascular disease.

Animal models are critically important for advancing our understanding of the infectivity, pathogenesis, and complications of SARS-CoV-2 infection and COVID-19 disease, including post-acute sequelae of COVID-19, and for accelerating pre-clinical testing of vaccines and therapeutic agents for humans.[2007] Investigators at Mutant Mouse Resource and Research Centers supported by ORIP, as well as other research centers, are developing mouse models that can faithfully mimic human disease conditions by

[2006] https://orip.nih.gov/about-orip/research-highlights/severe-combined-immunodeficient-pigs-promising-model-human-stem-cell

[2007] https://orip.nih.gov/animal-models-and-resources-coronavirus-research#rodents

expressing human orthologous genes, carrying mutations relevant to COVID-19, or testing genetic diversity.[2008] New mouse models and the testing platform are also being made readily available for use by other researchers. These will help swiftly assess the in vivo consequences of not only newly appearing SARS-CoV-2 variants that escape current therapeutic and vaccine strategies, but also of future viruses with similarly high-impact pandemic potential. For example, mouse models of the *SLC6A20* gene (which encodes an amino acid transporter that interacts with the main receptor for SARS-CoV-2) will allow researchers to explore susceptibility to and protection from COVID-19 respiratory failure for different blood types.[2009]

Working collaboratively, the seven ORIP-supported National Primate Research Centers (NPRCs) formed working groups and developed a Coronavirus Evaluation Network to investigate SARS-CoV-2 pathogenesis, developed an NHP model of COVID-19 and assays to detect SARS-CoV-2 in NHPs, and effect vaccine and therapeutic development.[2010] The NPRCs have developed more than 42 detailed standard operating procedures that have been harmonized across the NPRCs, including the NHP Field Guide on the NCATS Open Data Portal (for use by the research community), and they have worked with a NHP Coordinating Center for COVID-19 studies to facilitate research progress by coordinating data collection and analysis among sites. The NPRCs are also testing the effectiveness of a second-generation vaccine, determining the ability of inhaled monoclonal antibodies to treat COVID-19, and pursuing a collaborative project to investigate and compare post-acute sequalae of COVID-19 in three NHP species: African green monkeys, baboons, and rhesus macaques.

ORIP supports several nonhuman primate (NHP) resources, including the NPRCs, the Caribbean Primate Research Center, specific pathogen-free macaque and baboon colonies, vervet and squirrel monkey resources, and NHP antibody resources.[2011,2012,2013] These resources provide NHPs and related tools to support preclinical and translational research in areas such as infectious diseases, neuroscience, metabolic and digestive medicine, reproductive sciences, respiratory and cardiovascular sciences, and regenerative medicine.[2014] Genetic manipulations of adult animals have led to the development of an NHP model of Alzheimer's Disease for testing possible treatments.[2015,2016] Also, HIV research enabled by ORIP-supported NHP models included progress on vaccine development, cure strategies, and new treatments, including potential treatments to prevent HIV infection in newborns.

[2008] https://www.mmrrc.org/catalog/covid_models.php
[2009] Lee JW, et al. *Dev Growth Differ* 2021;63(3):219-227. PMID: 33595856.
[2010] https://orip.nih.gov/animal-models-and-resources-coronavirus-research#NonhumanPrimates
[2011] https://nprcresearch.org/primate/
[2012] https://orip.nih.gov/about-orip/research-highlights/macaques-humans-and-genomes-mgap-new-genetic-webtool-discover-natural
[2013] https://www.nhpreagents.org/, https://orip.nih.gov/sites/default/files/ORIP_Nonhuman_Primate_Resources_Fact_Sheet.pdf
[2014] https://orip.nih.gov/resource-directory/specific-pathogen-free-macaque-consortium
[2015] https://orip.nih.gov/about-orip/research-highlights/california-national-primate-research-center-team-develops-novel-tau-model-alzheimers-disease
[2016] https://orip.nih.gov/about-orip/research-highlights/california-national-primate-research-center-team-develops-novel-tau-model-alzheimers-disease

The Alliance for Genome Resources is a platform that integrates six independent data resources for model organisms (including yeast, zebrafish, and fruit fly) to facilitate cross-organism comparisons and analyses. By investing in such open-access tools and databases, NHGRI fuels genomic advances at a more rapid pace by enabling scientists and clinicians from both small and large institutions to participate in genomics research without high-cost barriers to entry.[2017] In October 2019, NHGRI sought input from an external scientific panel of investigators for their recommendations regarding future funding and sustainability of the model organism databases, the Alliance, and the Gene Ontology Consortium.[2018] NHGRI is looking to work with other NIH ICs, along with other international funding agencies, to develop sustainable funding models that keep these resources relevant to the cutting edge of biomedical research, both genomics-focused and beyond.

Figure 61. NHGRI Zebrafish core. Credit: NHGRI

Workshops and Capacity Building

To ensure the future of U.S. competitiveness and innovation in biomedical research, NIH invests in a variety of programs and opportunities to develop, broaden, and enrich the skills of the Nation's biomedical research workforce. For example, NICHD's Population Dynamics Research Infrastructure Program aims to advance the field of population dynamics research, which focuses on the scientific study of human populations, reproductive health research, and population health research.[2019] The program has several key objectives, one of which is to support career development experiences for junior population

[2017] Kishore R, et al. *Database (Oxford)* 2020;2020:baaa037. PMID: 32559296.
[2018] https://www.genome.gov/Funded-Programs-Projects/Computational-Genomics-and-Data-Science-Program/The-Alliance
[2019] https://www.nichd.nih.gov/about/org/der/branches/pdb

dynamics scientists that will contribute to their research independence.[2020] For more information on workforce recruitment, training and retention, please see Chapter 1.

The NNLM Center for Data Services (NCDS), established by NLM, provides training and resources to increase data science capacity among information professionals.[2021] NCDS focuses on developing individual data-related skills and expertise, with an emphasis on increasing capacity in underrepresented populations. These activities support NCDS's overarching goal of building data science and data services capacity for the health information community.

Providing access to and training on scientific tools is another way for NIH to support skills development. In 2021, NLM researchers released a project management framework for the next-generation sequencing (NGS) data analysis known as PM4NGS.[2022, 2023] NGS is a technology for studying the genetic variation associated with disease.[2024] NGS data analysis involves complex workflows and is typically performed by bioinformaticians with specialized training. PM4NGS, an open source, fully interactive tool for use on personal laptops or workstations, is designed for newly minted bioinformaticians. It can be used to train and guide users on how to organize and execute an NGS data analysis.

The structure of a molecule reveals important information about how it functions and can help scientists identify potential new therapeutic targets for vaccines and drugs to combat diseases and conditions. Cryo-electron microscopy (cryo-EM) is a method used to image frozen biological molecules, such as proteins and nucleic acids, without the need for structure-altering dyes or crystallization. The NIH Common Fund's Transformative High-Resolution Cryo-electron Microscopy Program[2025] funded the National Network for Cryo-electron Tomography[2026] as part of its initiative to advance the application of cryo-electron tomography (cryo-ET). This network offers researchers access and training, at no cost, on a specialized cryo-EM technique that is uniquely capable of visualizing intact regions of cells and tissues at high resolution and with little perturbation. The National Network for Cryo-ET was established with four service centers, including one service center that also serves as the central network hub.[2027] This initiative complements the program's existing three service centers by offering, also at no cost, access and training for cryo-EM data collection.[2028]

In 2020, NCATS and FDA's Center for Biologics Evaluation and Research (CBER) co-hosted a Workshop on Expanding adeno-associated virus (AAV) Manufacturing Capacity for Rare Disease Gene Therapies.[2029] At the meeting, thought leaders, key stakeholders, and innovators explored obstacles and identified

[2020] https://www.nichd.nih.gov/research/supported/PDRIP
[2021] https://nnlm.gov/about/centers/ncds
[2022] Vera Alvarez R, et al. *Gigascience*. 2021 Jan 7;10(1):giaa141. PMID: 33410471.
[2023] https://intramural.nih.gov/search/searchview.taf?ipid=121584&nidbreload=true
[2024] Behjati S and Tarpey PS. Arch Dis Child Educ Pract Ed. 2013 Dec; 98(6): 236–238. PMID: 23986538.
[2025] https://commonfund.nih.gov/CryoEM
[2026] https://www.cryoetportal.org/
[2027] https://www.cryoemcenters.org/cryoet-centers/
[2028] https://www.cryoemcenters.org/cryoem-centers/
[2029] https://www.ninds.nih.gov/news-events/events/expanding-aav-manufacturing-capacity-rare-disease-gene-therapies-workshop

opportunities for expanding the capacity of AAV manufacturing for rare disease gene therapies. Gene therapy, a technique that modifies a person's genetic material to treat or cure disease, holds promise for millions of patients who suffer from rare diseases. AAV-based vectors are the most commonly used delivery system for gene therapies currently under development. Therefore, it is critical to increase AAV manufacturing capacity to keep pace with the demand for AAV gene therapy clinical trials.

NCATS Day 2019: Conversations on Responsible Data Sharing provided a forum for various stakeholders in the translational science community to engage in robust dialogue about how to make scientific data as available as possible while ensuring the confidentiality and autonomy of research participants.[2030] Attendees considered data sharing from different viewpoints, including those of the research participant, community, researcher, federal funder, and the industry. The event featured thoughtful discussion, diverse perspectives, and insights into data sharing, which will help facilitate the translation of research results into new prevention strategies and treatments.

Pathways to Prevention (P2P) Program is a workshop series hosted by ODP to identify research gaps in a scientific area of broad public health importance through an unbiased, evidence-based process.[2031] P2P workshops bring together federal agencies, researchers, and community members to tackle topics that have incomplete or underdeveloped research and where there is a need for critical assessment of evidence. Recent workshops focused on a diverse range of topics, including Achieving Health Equity in Preventive Services (2019),[2032] Can Physical Activity Improve the Health of Wheelchair Users? (2020),[2033] and Improving Rural Health Through Telehealth-Guided Provider-to-Provider Communication (2021).[2034]

Scientific expertise underpins all of NIH's activities, such as the workshops and meetings highlighted above. NIH actively seeks out and leverages scientific expertise to advance its mission. ODP has developed the Prevention Research Expertise Survey (PRES) to build a directory of experts in research methods and study designs. PRES provides a process for identifying methods experts in the extramural community and characterizing their levels of expertise on a variety of research methods and in a variety of content areas related to prevention.[2035] ODP uses the PRES data to help NIH staff identify methodologists for recruitment to review panels, workshops, or other activities. It is part of ODP's ongoing work to improve the rigor and reproducibility of the prevention research conducted and funded by NIH.

[2030] https://ncats.nih.gov/news/events/ncats-day-2019#:~:text=NCATS%20Day%202019%2C%20held%20on,that%20can%20improve%20human%20health
[2031] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention
[2032] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/achieving-health-equity-preventive-services
[2033] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/can-physical-activity-improve-health-wheelchair-users
[2034] https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/improving-rural-health-through-telehealth-guided-provider-provider-communication
[2035] https://prevention.nih.gov/research-priorities/prevention-research-expertise-survey-pres

Chapter 4 Centers of Excellence

NIH Centers of Excellence programs are diverse in focus, scope, and origin. In general, they facilitate and coordinate research efforts on a specific disease, group of diseases, or area of research. Some were created as NIH-wide initiatives, others by individual ICs and offices within the NIH OD. Some reflect mergers or redesignations of existing programs, while others were mandated by Congress. The NIH Centers of Excellence programs described in this report are a subset of those established by statutory mandate.

Alzheimer's Disease Research Centers

Establishment of the Alzheimer's Disease Research Centers

There has been substantial interest from Congress and the public regarding research that focuses on AD and ADRD, including on the causes, diagnosis, treatment, and prevention of the diseases, as well as on disparities in cost and coordination of care. In 1984, Congress directed NIH, and in particular NIA, to foster further research related to AD, and it authorized the formation of the NIA Alzheimer's Disease Research Center (ADRC) program by the *PHS Act*, Section 445.

The first ADRCs were established through NIH funding in the mid-1980s in response to the Congressional directive, but also in reaction to information on AD/ADRD that was emerging from the work of NIH grantees and other researchers, and further incentivized by the prospect of a medical and social crisis being triggered by an explosion of AD/ADRD cases due to population aging. Although each center has its own emphasis, the ADRC's program's principal objective is threefold: to conduct cutting-edge basic, clinical, translational, and social/behavioral research; to train the next generation of researchers; and—as important—to provide the public with information 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 both better understand the causes of AD/ADRD and to develop and test new interventions for the diagnosis, treatment, and prevention of AD and other age-related neurodegenerative diseases.

In 2020, NIA established four new "Exploratory ADRCs" that are intended to broaden the geographic, scientific, and demographic groups and approaches included in current ADRC research initiatives,[2036] specifically seeking to include more people from underrepresented populations such as African Americans, Native Americans, and those in rural communities, whose members have different risk factors for developing AD/ADRD. The funding for the new exploratory centers enables investigators at those locations to build the infrastructure and to develop the partnerships needed to become part of the existing network. The four centers each have a unique scientific focus based on their local interests and communities.

[2036] https://www.nia.nih.gov/news/nih-expands-nations-alzheimers-and-related-dementias-research-capacity

How the ADRCs Function Within the NIH Framework

NIH currently funds 33 ADRCs, four Exploratory ADRCs, the National Alzheimer's Coordinating Center (NACC),[2037] which coordinates data collection and fosters collaborative research among ADRCs (Table 1). NIH also funds the National Centralized Repository for AD/ADRD (NCRAD), which is a national resource where clinical information and biological materials[2038] (such as DNA, plasma, serum, RNA, cerebrospinal fluid, cell lines and brain tissue) can be stored and requested. NCRAD serves as a biorepository that includes samples from individuals with AD/ADRD as well as from healthy controls. Funding for the ADRCs comes from NIA through the P30 center core grant mechanism. Each ADRC is funded for five years (Exploratory ADRCs are funded for three years), and ADRCs compete through a peer review process for additional funding. New applicants for ADRC funding compete with existing grantees.

Description of Disease or Condition

AD is the most common form of dementia among older people. It is an age-related, irreversible brain disorder that develops over many years. In its earliest stage, people experience memory loss or other behavioral or cognitive changes, which are usually mild and often mistaken for the sort of changes that can occur during the normal aging process. As the disease progresses, however, these symptoms often become more pronounced, indicating an advance to dementia, a condition characterized by marked memory loss and accompanied by behavior and personality changes. AD can also lead to decline in other cognitive abilities (such as decision making and language skills), eventually to an inability to recognize family or friends, and to severe mental decline. We are learning that the observed symptoms of AD are likely related to more than one underlying biological cause.

Other forms of dementia include Lewy body dementia,[2039] frontotemporal disorders,[2040] and vascular dementia.[2041] It is common for people to have mixed dementia,[2042] which is a combination of two or more types of dementia. For example, some people have both AD and vascular dementia.

Part of the value of the ADRCs is their ability to bring neuropathological and clinical data from annual patient visits together with biomarker and genetic data, providing a powerful platform for understanding the complex etiology of AD and other forms of dementia.

The most important known risk factors for the development of AD are biological age and family history, although education, diet, and environment appear to also play a role. Scientists have found that some of the risk factors for heart disease and stroke, such as high blood pressure, 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,[2043] and these lifestyle factors are being actively and rigorously

[2037] https://naccdata.org/
[2038] https://ncrad.iu.edu/
[2039] https://www.nia.nih.gov/health/what-lewy-body-dementia-causes-symptoms-and-treatments
[2040] https://www.nia.nih.gov/health/what-are-frontotemporal-disorders
[2041] https://www.nia.nih.gov/health/vascular-dementia
[2042] https://www.nia.nih.gov/health/what-is-dementia
[2043] https://www.nih.gov/news-events/news-releases/combination-healthy-lifestyle-traits-may-substantially-reduce-alzheimers

studied in clinical trials as possible interventions. Concurrently, the mechanisms underlying the observed effects of AD are under investigation in the laboratory**.**

Considerable progress in the understanding of AD has been made in recent years specifically because of the additional funding the field has received. This better understanding of the mechanisms, risk factors, and opportunities for intervention, means that we can have increased hope for treatments for AD.

Burden of Illness

Nearly 6.5 million Americans, most of them age 65 or older, are estimated to be living with AD, the most common form of dementia.[2044] Many others have an AD-related form of dementia. Experts agree that these numbers will increase significantly if no effective prevention or treatment methods emerge, and current U.S. demographic trends continue. The greatest risk factor for Alzheimer's is age. The number of people with the disease doubles for every 5-year interval beyond age 65, and the American population is indisputably aging. The U.S. Census Bureau estimates that the size of the population age 65 and older will increase to about 72 million people in the next 25 years. Moreover, the fastest-growing segment of the U.S. population consists of people ages 85 years or older.

Economic costs of AD are also considerable: According to one recent estimate, total payments in 2022 (in 2022 dollars) for all individuals with Alzheimer's or other dementias are estimated at $321 billion, not including the value of informal caregiving. Medicare and Medicaid are expected to cover $206 billion, or 64 percent, of the total health care and long-term care payments for people with Alzheimer's or other dementias. Out-of-pocket spending is expected to be $81 billion, or 25 percent of total payments.[2045] Dementia-related costs are expected to rise dramatically in the coming decades as the baby boom generation ages. The National Advisory Council on Aging (NACA) has recently approved in concept a new initiative to better estimate current costs of dementia and to model future expenses.

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/ADRD entered a new and significantly expanded phase in 2011 with the passage of the *National Alzheimer's Project Act (NAPA)*.[2046] The law renewed and strengthened national efforts to find effective treatments for AD and to support those with dementia, as well as their caregivers. The 2012 *National Plan to Address Alzheimer's Disease* outlined objectives and set milestones toward achieving these goals. Updated annually, the plan is a continually reevaluated framework that helps focus collaborative efforts to provide better clinical care and to improve services for those with the disease and their families, in addition to also recommending expanded research.[2047] NIH progress toward achieving the research milestones that have been developed under the auspices of NAPA is tracked through periodic review of

[2044] Rajan KB et al. *Alzheimers Dement* 2021;17(12):1966-1975. PMID: 34043283.
[2045] https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf.
[2046] http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf.
[2047] http://aspe.hhs.gov/2014-national-alzheimers-disease -plan-available.

the research funded, results achieved, and new initiatives and programs. Progress is reported through the NIA's AD+ADRD Research Implementation Milestones Database.[2048]

Planning for AD research expenditures evolved further in 2015 with the creation of the first NIH Bypass Budget for Alzheimer's and Related Dementias (then presenting a budget for FY 2017). Known as the "Bypass Budget" because it is presented without modification through the traditional federal budget process, this important document is redeveloped each year 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 and Congress on an annual basis. Strategic planning efforts informing the annual development of this budget include the following:

- Alzheimer's Disease Research Summits: 2012, 2015, 2018, and 2021
- Alzheimer's Disease-Related Dementias Conferences: 2013, 2016, 2019, and 2022
- Alzheimer's Care Services, and Support Summits: 2017, 2020, 2023
- A 2013 meeting on Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome, a uniquely vulnerable population
- The AD/ADRD Research Implementation Milestones

The ADRC program supports the goals outlined in the *NAPA* plan and the Bypass Budget, providing infrastructure and core resources to enhance ongoing research by supporting a multidisciplinary environment that includes basic biomedical, behavioral, social, clinical, and translational scientists to study the causes, progression, prevention, diagnosis, and treatment of AD/ADRD and to improve health care delivery. In addition, the ADRC network provides an infrastructure to facilitate activities across NIA signature programs, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), AMP-AD, and the Alzheimer's Clinical Trials Consortium (ACTC).[2049] ADRCs also foster the development of new research approaches and provide training opportunities for research fellows and junior faculty who are interested in conducting interdisciplinary AD/ADRD research.

In 2017, in partnership with leading experts from academia, industry, and the nonprofit world, NIA completed a strategic planning process[2050] that was intended to generate guidance for the ADRCs in supporting the integrated translational research agenda that had emerged from the various summits and which is outlined in the National Plan's research implementation milestones. NACA used the information gathered through this process to develop a set of recommendations that address all aspects of the ADRC program, including clinical research capacities, thus maximizing the value of the unique neuropathological expertise across the ADRCs, translational research, interactions and networking, infrastructural support, and training. NIA has implemented several the recommendations and is actively tracking progress on successful completion of the goals outlined in the recommendations.

[2048] https://www.nia.nih.gov/research/milestones.
[2049] https://www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc
[2050] https://www.nia.nih.gov/news/expert-panel-offers-transformative-recommendations-nih-alzheimers-research-centers

Resource Sharing

Resources shared from the ADRCs include data (through the NACC), biological samples (through the NCRAD), and brain MRI and positron emission tomography (PET) (through Standardized Centralized Alzheimer's and Related Dementias Neuroimaging [SCAN]).

National Alzheimer's Coordinating Center

In 1999, NIH established the NACC to facilitate collaborative research and standardize procedures among the ADRCs. NACC has developed and maintains a large database of the standardized clinical and neuropathological research data that has been collected from each ADRC. This database is a valuable resource for both exploratory and explanatory AD research. The data provided by the NACC supports large studies that use participant samples from multiple ADRCs reflecting populations that are ethnically, racially, and geographically diverse. A minimum dataset of 67 variables collected from the ADRCs contains data on more than 74,000 people who have been enrolled since 1984. A much richer longitudinal uniform dataset (comprising 725 variables) has been collected from the more than 45,000 participants enrolled since 2005. NACC itself has funded 24 collaborative multicenter studies, 21 junior investigator awards to use NACC data, and six new investigator awards to promote young investigator development, as well as the more than 1,450 publications that have utilized NACC data. Currently, NACC is averaging 40 data requests per month from both national and international investigators.

In 2013, NACC began accepting voluntary contributions of brain images from ADRCs. More than 7,000 images from more than 5,200 subjects, 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 further linked to the genotype data from the Alzheimer's Disease Genetics Consortium (ADGC)[2051] when that data becomes available and when appropriate consent has been obtained. Further information is available on the NACC website.

Today, the NACC database is one of the largest and most comprehensive databases of its type in the world. Data collected by NACC are freely available for all scientists to use in research studies directly and are also made 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.

National Centralized Repository for Alzheimer's Disease and Related Dementias

NCRAD, hosted by Indiana University, collects and shares blood, DNA, cell lines, and other biospecimens from more than 100,000 research participants at the ADRCs and in other NIA-funded studies.[2052] More than 350,000 samples have been shared with qualified researchers. NCRAD also works directly with the NIH Alzheimer's Disease Genetics Initiative, which was established to identify genetic risk factors for late-onset AD, and ADGC, which conducts large-scale whole-genome studies on AD. ADGC itself maintains one of the largest collections of samples available for genome-wide association studies of AD, a resource that

[2051] https://www.adgenetics.org/
[2052] https://ncrad.iu.edu/

is being used to identify the susceptible and protective genes that influence the onset and progression of late-onset AD. These samples are especially valuable because of the rich clinical data that is associated with each participant. ADGC is also part of the International Genetics of Alzheimer's Project, a multinational collaboration established in 2011 to identify and map genes that contribute to the disease.

Standardized Centralized Alzheimer's and Related Dementias Neuroimaging

In 2020, NIA established the SCAN[2053] initiative with the goal of standardizing the acquisition, curation, and analysis of PET and MRI images acquired through the ADRCs. Through SCAN, ADRCs upload images to a portal in the Laboratory of Neuroimaging at the University of Southern California where the images are de-identified. The images are then processed for quality assurance and harmonization at the PET and MRI laboratories at the University of Michigan and Mayo Clinic. Uploaded images are further analyzed by the PET laboratory at UC Berkeley and the MRI laboratories at Mayo Clinic and UC Davis. Harmonized images and other data are available to qualified investigators through NACC. Results are returned to the ADRCs and made available to researchers via the NACC database.

Much of the progress in AD research in the U.S. during the past 40 years stems from research conducted at or resources provided by the ADRCs. ADRC scientists have conducted a significant amount of the research on protein processing related to plaque and tangle formation in the brain, now well-known hallmarks of AD. ADRC researchers have also identified the common properties of the abnormal proteins associated with several other neurodegenerative diseases. In recent years, ADRC researchers have evaluated cognitive changes associated with normal aging and the transitions to mild cognitive impairment (early difficulties with thinking and remembering) and with dementia.

With this research has come a more precise understanding of the timing of various types of cognitive change, as well as the development of better ways to measure and evaluate those changes. ADRC researchers have also identified lifestyle factors that contribute to changes in cognitive abilities, such as social and physical activity.

Each of the ADRCs has a neuropathology core and offers the opportunity for autopsy consent to all participants. The National Alzheimer's Coordinating Center has data on more than 18,000 deceased participants whose brain tissue and associated data is available to researchers. This valuable resource has contributed tremendously to research in AD/ADRD and to our understanding of the many different causes of cognitive impairment.

An important priority for the ADRCs is to recruit racially and ethnically diverse participants for AD research. Certain centers focus on special populations, including on African American, Hispanic, Native American, and Asian American participants. NACC data now show that approximately 20 percent of people enrolled in the ADRCs are non-White.

All ADRCs have Outreach, Recruitment, and Engagement Cores that provide outreach to the public and facilitate participant recruitment for large-scale national projects, such as NIA's Genetics Initiative, ACTC, and ADNI, as well as for clinical trials. Collaborations include ongoing interactions with organizations such

[2053] https://scan.naccdata.org/

as the Alzheimer's Association, the HHS Administration on Aging, and NIH's Alzheimer's Disease Education and Referral Center. The ADRCs pay special attention to issues of cultural sensitivity and, where appropriate, structure information to effectively reach diverse populations, including people for whom English is not a first language.

In 2019, NIA unveiled the Alzheimer's and Dementia Outreach, Recruitment, and Engagement Resources (ADORE) website,[2054] a repository of materials submitted by ADRCs and other organizations to support recruitment and retention of participants for clinical trials and studies. ADORE includes recruitment plans, videos, articles, toolkits, and more. The unique experience of these ADRCs was also instrumental in the development of NIH's National Strategy for Recruitment in Participation in Alzheimer's and Related Dementias Clinical Research,[2055] along with its companion Recruitment Planning Guide,[2056] which was released in October 2018. In addition, the two most recently funded ADRCs (at Duke University/University of North Carolina and the University of Texas) share a focus on identifying ways to understand and diminish the burden of these diseases on understudied groups, specifically Mexican American Hispanics and Black/African Americans.

NIH Funding for FY 2019, 2020, and 2021

NIH Funding of ADRCs for FY 2019, FY 2020, and FY 2021: $76.55 million in FY 2019, $90.18 million in FY 2020, and $103.30 million in FY 2021.

FY 2019, FY 2020, and FY 2021 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments for the ADRCs include the following examples:

- *Developmental Projects.* Since 2019, each ADRC provides opportunities for investigators to start a research project each fiscal year. At the time of this report, 66 projects have been awarded, most of which explore the molecular pathogenesis and physiology of AD/ADRD.
- *Research Projects.* Prior to 2019, each ADRC provided resources for one, two, or three focused projects for basic or clinical biomedical, translational, and epidemiological, caregiving, educational or behavioral research. This is intended to allow an investigator an opportunity to develop preliminary data sufficient to provide the basis for an application for independent research support. The projects were designed for postdoctoral or junior faculty-level investigators but may be awarded to a more senior investigator who had experience in areas other the AD research and who wanted to work in the AD research field or who wanted to try a new hypothesis, method or approach that was not an extension of ongoing AD research. Overall, the ADRCs awarded 957 research projects from 2003–2018, most of which were related to the molecular pathogenesis and physiology of AD/ADRD.
- *Research Education.* Each ADRC is required to support educational activities that complement and enhance the development of a workforce to meet the nation's biomedical, behavioral, and clinical

[2054] https://www.nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources
[2055] https://www.nia.nih.gov/research/recruitment-strategy
[2056] https://www.nia.nih.gov/sites/default/files/2019-05/ADEAR-recruitment-guide-508.pdf

needs in dementia-related research. There are creative educational activities with a primary focus on providing research experiences to promote the development of future research leaders in the ADRC area of focus, particularly leaders who can integrate clinical insights with knowledge of advances in the basic and translational sciences to improve interventions for maintaining cognitive health and avoiding dementing disease conditions. Overall, 1,069 individuals representing seven different trainee levels (high school to junior faculty) have been provided with educational activities. More than 40 percent of the trainees have published a scientific manuscript, and more than 30 percent have presented at a scientific conference or meeting. In the future, trainee data presentations will be incorporated during ADRC meetings.

Research Activities and Outcomes

Since the establishment of the ADRC program in 1984, investigators have published thousands of research papers on all aspects of AD and related disorders. An analysis in 2014 identified more than 12,000 scientific papers based on ADRC research.[2057] Topics have ranged from the disease's biology to its impact on family and society and have included many studies of diagnosis and treatment. In addition, the ADRC program has demonstrated tremendous success in facilitating collaborations across institutions. An internal analysis demonstrated that collaborative multi-ADRC research articles are consistently cited more frequently than AD articles overall.

Research accomplishments include the following important studies performed by ADRC scientists, which highlight research carried out by several centers. These are only a few examples from a wide range of research studies conducted by the ADRCs, and they demonstrate the breadth of research that is supported by the ADRCs:

- *Brain stimulation: A new approach to AD treatment.* Alterations in gamma waves—a pattern of brain activity involved in cognitive functioning, learning, memory, and information processing—are associated with AD pathology in mouse models of the disease. ADRC investigators found that auditory stimulation of gamma waves with a series of tones improved cognitive performance in a mouse model of AD, and when combined with visual stimuli, the stimulation induced immune activity and reduced amyloid burden throughout the brain. Further studies are needed to determine whether this non-invasive approach is effective in humans.[2058]
- *ADRCs played a major role in redefining AD.* A clear definition of AD is necessary for developing effective prevention and treatment strategies. ADRC scientists were part of a team convened by the NIA and the Alzheimer's Association to develop a new "biological framework" for AD research. Before this framework was developed, AD was largely defined by pathology identified at autopsy, but this research has moved the definition of AD from autopsy to life. Although autopsy remains critical for research, the framework enables researchers to utilize biomarkers measured during life to study Alzheimer's from its earliest biological underpinnings through outward signs of memory loss and other clinical symptoms. The framework, published in 2018,

[2057] Hughes ME, et al. *JAMA Neurol* 2014;714:412-20. PMID: 24514750.
[2058] Martorell AJ, et al. *Cell* 2019 Apr 4;177(2):256-271. PMID: 30879788.

is already facilitating a more precise and efficient approach to testing drugs and other interventions.[2059]

- *Autopsies conducted at ADRCs enabled the description of a newly defined Alzheimer's-like brain disorder, LATE.* Named one of the top science stories of 2019 by *Discover Magazine*,[2060] ADRC investigators, in collaboration with international peers, defined a brain disorder that mimics clinical features of Alzheimer's disease: Limbic-predominant Age-related TDP-43 Encephalopathy (LATE). LATE is associated with misfolded TDP-43, a protein that normally helps to regulate gene expression in the brain and other tissues.[2061] A 2018 workshop, supported by NIA, produced classification guidelines for diagnosis and staging of LATE, as well as recommendations for future research directions.[2062] A follow-up workshop in 2022 provided updates on research progress and offered hope for new biomarkers.[2063] This newly defined disease helps to explain, in part, why previous trials aimed at amyloid may have failed: Some people in the trial actually had a different or additional disease processes. Learning more about LATE will help to develop treatments specific to this disease and enable better and more accurate diagnosis for older adults.
- *A new tool to measure synaptic loss in AD.* The ADRCs award small grants that allow young investigators to use the vast resources of the ADRC to generate preliminary data that will support larger projects. In 2015, the Yale ADRC funded one such grant to develop a technique using PET imaging in conjunction with a novel tracer that measures synaptic density. Synapses are the spaces between neurons, and people with AD have fewer synapses in specific parts of the brain. The researchers found that this newly developed method can be used to distinguish people with AD from people without, and they were able to use their preliminary data to compete successfully for additional funding to further develop the technique to measure disease progression.[2064] This tracer is now being used to measure treatment response in clinical trials.[2065] As the tracer is further developed and refined, it may provide another tool for understanding brain changes through the course of the disease, as well as for measuring whether certain types of drugs are working as expected. Better measurements can also reduce costs and length of clinical trials.
- *Building lasting relationships, one load of laundry at a time.* Characteristics that are unique to the ADRCs are their Outreach, Recruitment, and Engagement Cores, which serve as crucial liaison and engagement conduits among the ADRCs, those living with dementia and their caregivers, and the broader professional and general public communities. A key goal is to encourage more people, particularly in diverse populations, to participate in clinical research. For example, the community outreach team at the Rush Alzheimer's Disease Center in Chicago has developed innovative methods to build close relationships with local African American communities. During

[2059] Jack, C. R., et al. *Alzheimer's & Dementia* 2018;14(4):535–562. PMID: 29653606.
[2060] https://www.discovermagazine.com/mind/a-new-kind-of-dementia-strikes-the-oldest-old
[2061] Nelson PT, et al. *Brain*. 2019;142(6): 1503-1527. PMID: 31039256.
[2062] Nelson PT, et al. Op. cit.
[2063] https://www.nia.nih.gov/research/dn/late-2022
[2064] Chen M-K et al. *JAMA Neurol*. 2018 Oct 1;75(10): 1215-1224. PMID:30014145
[2065] https://reporter.nih.gov/search/6LEgBXtc0kmYEXaUxt_LrA/project-details/9863727.

the COVID-19 pandemic, team members held town hall meetings, organized personal protective equipment drives and webinars on their proper usage, and conducted food drives and delivery services. They also designed and hosted outreach and wellness events at local laundromats where people could wash their clothes for free. At these events, participants could learn more about AD, research, and the ADRC. The events were held *before* participants were invited to join a research study, and participation in the events was not contingent on participation in research. These events were important factors in building trust between ADRCs and the vulnerable populations they serve.[2066]

- Higher income is correlated with better health outcomes across the lifespan,[2067] and the mechanisms underlying this phenomenon are of considerable interest to researchers. However, collecting and sharing socioeconomic metrics at the neighborhood level has proved difficult for researchers across many fields. A team including researchers associated with the Wisconsin ADRC developed the Neighborhood Atlas,[2068] a free, user-friendly, online tool that enables customized ranking and mapping of neighborhoods according to socioeconomic disadvantage across the U.S., including Puerto Rico.[2069] Already, the Neighborhood Atlas has been used to link neighborhood disadvantage with brain changes suggestive of AD at autopsy[2070] and to uncover disparate AD burden in rural vs. urban Appalachian counties in Ohio,[2071] and it is increasingly being used as a tool to determine the role of place in the development of Alzheimer's and related forms of dementia.[2072]
- *The eyes have it: Vision change as a biomarker of early AD.* Early detection of "preclinical" AD—the period when pathology is present in the brain, but cognition is still normal—provides a window in which interventional trials can be initiated. Currently, the most reliable early detection can be complex and invasive, potentially involving cumbersome brain imaging and examination of spinal fluid. Visual problems and changes in the eye are common among adults with AD, so investigators at the Indiana ADRC assessed visual contrast sensitivity (the ability to distinguish objects from their background) in 74 older adults, including 31 cognitively healthy individuals and others at various stages of cognitive impairment, in order to determine whether a test for impaired visual contrast sensitivity could detect Alzheimer's when amyloid and tau abnormalities are just beginning to occur in the brain. Participants also underwent brain imaging to identify early brain changes related to Alzheimer's. In all participants, poorer visual contrast sensitivity was significantly associated with amyloid and tau deposits in certain parts of the brain, as well as a lower temporal lobe volume. These findings suggest that visual contrast sensitivity testing may detect very early-stage Alzheimer's more easily, less invasively and less expensively than

[2066] https://www.npr.org/sections/health-shots/2020/10/20/925493843/a-big-alzheimers-drug-study-is-proceeding-cautiously-despite-the-pandemic
[2067] See, for example, https://www.bls.gov/opub/mlr/2017/beyond-bls/pdf/income-and-health-outcomes.pdf
[2068] https://www.neighborhoodatlas.medicine.wisc.edu/
[2069] Kind AJH, Buckingham W. *New England Journal of Medicine*, 2018. 378: 2456-2458. PMCID: PMC6051533.
[2070] Powell WR et al. *JAMA Netw Open.* 2020;3(6):e207559. PMID: 32525547.
[2071] Wing JJ et al. *J Alzheimer's Dis* 76(4):1309-1316, 2020. PMID: 32597814.
[2072] https://aspenbrain.institute/blog-posts/alzheimers-research-looks-at-hot-spots-across-the-us

current imaging and spinal-tap methods. However, larger studies are needed to further test visual contrast sensitivity as a potential biomarker for Alzheimer's.[2073]

Recommendations for Improving ADRCs Effectiveness, Efficiency, and Outcomes

Evaluation Plans

The NACA evaluates and makes recommendations for the ADRC program on a regular basis, with the next evaluation tentatively planned for 2024. More broadly, NACA reviews the NIA Division of Neuroscience, which houses the ADRC program, every four years. The next Division of Neuroscience review will take place in 2023. Most recently, the ADRC Program was evaluated in 2017 by experts from academia, industry, and non-profit foundations who work on Alzheimer's and other complex diseases. This evaluation produced a comprehensive report recommending strategic revisions to the ADRC program that will enable it to achieve NAPA objectives by leveraging resources, capabilities, and research participants across the network.[2074] Lastly, the ADRC program has nine steering committees that continuously evaluate the different cores of the ADRC program and provide insight and feedback on opportunities for improvement and collaboration.[2075]

Future Directions

NIH plans to have the ADRCs continue to emphasize research related to the transition from normal aging to mild cognitive impairment to full-blown AD, as well as studies of the overlap between AD and other neurodegenerative diseases. Because recent studies, including ADRC studies, have suggested that disease processes common to several conditions may overlap in people with symptoms of dementia,[2076] a particular focus will be on the etiology, diagnosis, and treatment of mixed dementias. In addition, the ADRCs will continue to search for biomarkers—particularly fluid biomarkers, a priority identified in the most recent Division of Neuroscience Program Review—that predict cognitive decline and diagnose cognitive impairment and dementia. Further, the ADRCs will disseminate and utilize clinically valuable data that has been paired with neuroimaging, biospecimens, and biomarkers. The ADRC program will continue to increase diversity of Clinical Core research participants and prioritize identifying and addressing disparities among populations. Lastly, the ADRCs will continue to enhance opportunities for remote assessment among their research participants.

Table 1. Alzheimer's Disease Research Centers

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

[2073] Risacher SL et al. *Brain Commun* 2020;2(1):fcaa019. PMID: 32309804.
[2074] https://www.nia.nih.gov/news/expert-panel-offers-transformative-recommendations-nih-alzheimers-research-centers
[2075] https://naccdata.org/nacc-collaborations/committees
[2076] Boyle PA, et al. *Ann Neurol* 2017;83(1):74-83. PMID: 29244218.

Institution and Location	Year Established
University of Kentucky, Lexington, KY	1985
University of Pittsburgh, Pittsburgh, PA	1985
University of Washington, Seattle, WA	1985
Washington University in St. Louis, St. Louis, MO	1985
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
Rush University Medical Center, Chicago, IL	1991
Boston University Medical Campus, Boston, MA	1996
Northwestern University, Chicago, IL	1996
University of California, Irvine, CA	2000
Arizona Alzheimer's Center, Phoenix, AZ	2001
University of California, San Francisco, CA	2004
Emory University, Atlanta, GA	2005
University of Wisconsin, Madison, WI	2009
University of Kansas Medical Center, Kansas City, KS	2011
Stanford University, Stanford, CA	2015
Yale University, New Haven, CT	2015
University of Florida, Gainesville, FL	2015
University of Michigan, Ann Arbor, MI	2016
Wake Forest University, Winston-Salem, NC	2016
Cleveland Alzheimer's Disease Research Center, Cleveland, OH	2019
Cleveland Clinic Lou Ruvo Center for Brain Health Exploratory Alzheimer's Disease Research Center, Las Vegas, NV	2020
New Mexico Exploratory Alzheimer's Disease Research Center, Albuquerque, NM	2020
University of Alabama Exploratory Alzheimer's Disease Research Center, Birmingham, AL	2020
Vanderbilt Exploratory Alzheimer's Disease Research Center, Nashville, TN	2020
Duke/University of North Carolina, Durham, NC	2021
South Texas Alzheimer's Disease Research Center, San Antonio, TX	2021

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 (Table 2).

As Centers of Excellence in geriatrics research and training, the OAICs provide intellectual leadership in geriatrics research, encouraging and facilitating multidisciplinary and interdisciplinary collaborations in basic, translational, and clinical research relevant to older people's health and independence. In addition, each OAIC includes a research education component to provide research training and career development opportunities in geriatrics and related fields.

Description of Disease or Condition

Age is a primary risk factor for many disabling diseases and conditions. However, human aging is a highly variable process; no single disease or condition is synonymous with aging. Understanding the process of aging is necessary to promote the health and well-being of older adults. Research in aging focuses on a range of conditions, including geriatric syndromes (e.g., low muscle mass/strength, mobility disability, urinary incontinence) and diseases and disorders that are more common among older adults, such as cancer, cardiovascular disorders, stroke, and sensory impairment.

Burden of Illness

Currently, nearly 56 million Americans are 65 years of age or older. Of these, more than six million are 85 and older, and more than 80,000 have reached 100 years of age. By 2030, the number of individuals aged 65 or older is likely to reach 73 million. The number of the oldest of the old, people aged 85 or older, is expected to be more than 18 million by 2050.[2077]

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 the programs at each awardee institution in a key area of aging research; contribute to scientific understanding that promotes greater independence for older people; and offer opportunities for training and professional development for early-career scientists working in aging research. The program's overarching goal is to enhance translation of basic and clinical

[2077] Projected Age Groups and Sex Composition of the Population: Main Projections Series for the United States, 2017–2060. U.S. Census Bureau, Population Division: Washington, DC. Revised September 2018.

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 the NIA Research Centers Collaborative Network (RCCN)[2078] and other NIA-funded programs and centers (e.g., Resource Centers for Minority Aging Research,[2079] Centers on the Demography and Economics of Aging,[2080] Roybal Centers,[2081] ADRCs,[2082] and Nathan Shock Centers[2083]).
- 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 larger scale, regarding technology, methodology, analysis, or other expertise.

NIH Funding for FY 2019, 2020, and 2021

NIH funding for the OAICs was $14.34 million in FY 2019, $16.88 million in FY 2020, and $19.26 million in FY 2021.

FY 2019, FY 2020, and FY 2021 Progress Report

Programmatic Activities and Outcomes

- The University of Florida OAIC focuses on the optimization of physical performance and mobility in older persons, with the goal of maintaining independence among this population. University of Florida researchers examine these issues from interdisciplinary perspectives across the entire

[2078] https://www.rccn-aging.org/
[2079] http://www.nia.nih.gov/research/dbsr/resource-centers-minority-aging-research-rcmar
[2080] http://www.nia.nih.gov/research/dbsr/centers-demography-and-economics-aging
[2081] http://www.nia.nih.gov/research/dbsr/edward-r-roybal-centers-translation-research-behavioral-and-social-sciences-aging
[2082] http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers
[2083] http://www.nia.nih.gov/research/dab/nathan-shock-centers-excellence

spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral and social sciences, and epidemiology.

- The Boston OAIC fosters collaborations among multidisciplinary teams of investigators from Harvard Medical School, Boston University, and Tufts University to foster function-promoting therapies, or pharmacologic, physical, nutritional, technological, and behavioral interventions that reduce the burden of disabling functional limitations in older adults.
- The University of Pittsburgh OAIC provides support and resources for investigators to identify interventions to optimize mobility and balance and prevent fall-related injuries in the elderly. This OAIC provides an integrated, multidisciplinary approach by pooling resources from five schools at the University of Pittsburgh. The OAIC is currently conducting several studies of interventions to improve balance and mobility, prevent falls, and prevent fall-related injuries.
- The goal of the Duke University OAIC is to understand and optimize reserve and resilience among older adults. Investigators at the Duke OAIC conduct translational studies to understand and enhance people's ability to withstand or recover from functional decline following acute or chronic health stressors.
- The Johns Hopkins University OAIC supports research to determine the causes of and potential interventions to reduce frailty in older adults. A major recent focus of research has been the characterization of potential causes of frailty, as well as pharmacological and behavioral interventions.
- The University of Maryland, Baltimore OAIC is studying rehabilitation approaches that involve exercise and motor learning. The goal is to improve the recovery of older adults who have suffered a stroke, hip fracture, or other chronic debilitating condition. The OAIC plans to translate these findings into effective community-based rehabilitation programs.
- Research at the University of Texas Medical Branch OAIC focuses on identifying predictors of physical function and recovery from illness in older adults, identifying novel treatments to improve function and accelerate recovery, and using clinical trials to assess the efficacy of these treatments in older patients.
- The Wake Forest University OAIC's mission is to assess the risk factors for physical disability in older adults and to develop and test effective preventive interventions, with an emphasis on risk factors and preventive interventions focusing on skeletal muscle. Wake Forest also hosts the Coordinating Center for the National Claude D. Pepper Center Program.
- The Yale University OAIC's research focuses on investigating geriatric health conditions that have multiple causes. This focus includes single conditions resulting from several contributing factors or affecting several outcomes, as well as multiple co-occurring conditions.
- The University of Michigan OAIC, the first OAIC funded by NIH, advances research on the health care problems of older adults. Its current research focuses on understanding how metabolic factors and inflammation interact with age-related diseases and comorbidities, to determine key health outcomes related to mobility and functional status. The OAIC is also pursuing translational research on the interaction of metabolic factors and inflammation with age-related diseases and comorbidities, with the goal of improving health outcomes related to mobility and functional status.

- The Mount Sinai School of Medicine OAIC focuses on pain management and palliative care. Investigators with this center conduct pilot and exploratory studies aimed at understanding and ameliorating pain in older adults. The Mount Sinai OAIC is also developing the infrastructure for population-based research on pain and palliative care.
- The University of California, San Francisco OAIC focuses on disability in older people. Its investigators are exploring what leads to disability, how to prevent disability, and how to ameliorate the impact of the disability on patients and caregivers. This OAIC is particularly interested in the needs of the most vulnerable elders, whether they are vulnerable because of complex medical circumstances or because of adverse social circumstances.
- Translation of basic research findings into clinical interventions that will benefit older Americans is the focus of the new OAIC at the University of Texas Health Science Center at San Antonio. Current pilot projects include both preclinical and clinical studies.
- The mission of the newly established OAIC at Northwestern University is to improve primary care management for older, more medically complex adults with multiple chronic conditions. (According to the Centers for Disease Control and Prevention, more than 56 percent of adults aged 65 and older have two or more chronic health conditions, and more than 23 percent of adults aged 65+ have three or more chronic conditions.[2084])
- Recognizing the wide variability among how individuals age, the OAIC at the University of Connecticut's focuses on precision gerontology and seeks to leverage an understanding of the growing heterogeneity of aging into interventions rendered more effective by being better targeted.

Research Activities and Outcomes

- Nearly half of American adults have hypertension (defined by the American College of Cardiology/American Heart Association as mean systolic blood pressure ≥130 mm Hg, mean diastolic blood pressure ≥80 mm Hg, or current use of antihypertensive medication).[2085] Deintensification of antihypertensive medication may be possible for some people when tight control of systolic blood pressure (SBP) is achieved. However, due to the frequent exclusion of older adults with multiple chronic conditions from relevant clinical trials, little is known about the benefits or harms of deintensification of medication in this population. In an observational study, investigators with the University of Michigan OAIC analyzed EHR data from more than 228,000 veterans aged 65 and older with well controlled hypertension. The study took place over nine months and sought to determine whether clinical outcomes differed with respect to cardiovascular events, syncope (fainting), or fall injury when antihypertensive treatment intensity was modified. The investigators found that antihypertensive treatment deintensification in older patients with tightly controlled SBP was associated with worse outcomes than maintaining the same treatment intensity. The investigators note that patients' health may have been declining over the course of the study, potentially both triggering treatment deintensification and contributing to adverse health effects, and that more controlled clinical trials are needed to gain

[2084] https://www.cdc.gov/nchs/health_policy/adult_chronic_conditions.htm
[2085] https://www.cdc.gov/bloodpressure/facts.htm

a clearer picture of the risks and benefits of treatment deintensification in older adults with comorbidities.[2086]

- Perceived physical fatigability, or whole-body tiredness linked to quantifiable effort or tasks, provides a sensitive patient-reported metric for physical limitations associated with fatigue. The only validated instrument to measure perceived physical fatigability, the Pittsburgh Fatigability Scale (PFS), was developed by investigators at the University of Pittsburgh OAIC and the NIA Intramural Research Program. Recently, NIA-supported investigators administered the PFS to participants in the Long Life Family Study, an international multicenter study of exceptional longevity, in order to evaluate the instrument's prognostic value as an independent predictor of mortality risk. They found that perceived physical fatigability as measured with the PFS is a robust independent indicator of mortality risk in older adults. In this study, the most severe perceived physical fatigability (PFS scores ≥ 25) was associated with a 2.3-fold higher risk indicator of death over 2.7 years follow-up compared with less fatigability, even after adjustment for age and sex (two strong independent predictors of mortality). These findings extend previous work showing that global fatigue, a less-sensitive measure of one's perception of fatigue, which does not contextualize fatigue to activity, predicted excess mortality over a much longer period of time (7-20 years).[2087]
- Between five and seven percent of older Americans report severe financial strain, defined as substantial difficulty meeting their basic needs. Severe financial strain is associated with lower medication adherence, which may affect recovery from acute medical conditions such as myocardial infarction (AMI). Investigators at the Yale OAIC analyzed data from a longitudinal cohort study of U.S. adults aged 75 and older to determine the relationships between financial strain and recovery from AMI and found that severe financial strain was associated with a higher risk of death in the six months following hospital discharge, even after controlling for sex, medical complexity, and functional and mobility impairment. Although the specific reasons for this association were unclear, screening for financial strain provides an opportunity to provide at-risk elders with community supports that may facilitate recovery and reduce risk of adverse medical outcomes.[2088]
- Older adults are particularly vulnerable to herpes zoster (shingles). While protective vaccination against shingles is available, its effectiveness—specifically in frail elders—had not been established. Vaccines against other infections are often less effective in older or frail individuals, and older persons are frequently under-represented in randomized controlled trials. Investigators from the Duke University OAIC were part of an international team that analyzed data from two previously conducted phase 3 clinical trials of the Shingrix recombinant zoster vaccine. They created and applied a new frailty index for participants (all over 70 years old) and assessed vaccine efficacy and safety and immune response across frailty subgroups. They found that the vaccine was safe and highly effective in preventing shingles infection in older persons regardless of frailty

[2086] Aubert CE et al. *J Am Geriatr Soc* 2021;69(10):2831-2841. PMID: 34097300.
[2087] Glynn NW et al. *J Gerontol A Biol Med Sc 2022;*77(4): 837-841. PMID: 34908118.
[2088] Falvey, JR et al. *JAMA Intern Med* 2022; 182(4):445-448. PMID: 35188537.

status. These results provide valuable information for older adults, particularly frail elders, about the benefits of vaccination against herpes zoster with existing vaccines.[2089]

- Hospital at Home care (HaH), or hospital-level care at home as a substitute for in-hospital acute care, has been shown in clinical studies to generate similar or better clinical outcomes and greater patient and caregiver satisfaction. Although previous studies have suggested that HaH care is also less expensive than traditional hospital care, most of those studies were small, were conducted outside the U.S., or did not include post-acute care. In a large-scale demonstration project, investigators at the Mount Sinai OAIC offered HaH to 300 patients (representing more than 500 hospitalizations), including 30 days of post-acute follow-up, and compared costs with those of similar patients who either declined HaH or to whom HaH was not offered. They found that HaH care cost several thousand dollars less compared to standard inpatient care, and that the cost savings persisted after adjusting for multiple patient characteristics. These findings add to the growing body of evidence that substituting inpatient care with HaH, where appropriate, may reduce healthcare costs while maintaining both clinical outcomes and patient satisfaction.[2090]

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the OAICs

In 2015, the NACA reviewed the NIA Division of Geriatrics and Clinical Gerontology, where the OAICs are administratively housed, and made several relevant recommendations,[2091] including the following:

- Facilitate translational efforts by creating a mechanism to bring together directors of all NIA-sponsored centers (e.g., Pepper, Shock, Roybal, Alzheimer's, Minority Aging, Demography) and possibly some non-NIA centers, around critical themes that cross divisions, and sponsor post-meeting funding initiatives that mandate investigators from different fields.
- Leverage partnerships by supporting interactions of the Claude D. Pepper Centers with other NIA-sponsored centers.

In 2018, NIA established the RCCN.[2092] Led by the American Federation for Aging Research and investigators at Wake Forest School of Medicine, RCCN is a new resource that aims to bridge the programs of NIA's six centers[2093] and promote collaborations across center areas. The program supports five complementary strategies:

- *Workshops* provide an environment to share views among scientists from different disciplines and to explore common problems from different perspectives. Recent RCCN workshops have focused on health disparities and aging, sex and gender differences in aging, measuring biologic age, and resilience and reserve.

[2089] Curran D et al.. *J Am Geriatr Soc* 2021; 69(3):744-752. PMID: 33197294.
[2090] Saenger PM et al. *J Am Geriatr Soc* 2022; 70(5):1374-1383. PMID: 35212391.
[2091] The next NACA review of DGCG activities, including the OAICs, will be in 2023.
[2092] https://www.rccn-aging.org/
[2093] In addition to the OAICs, NIA supports the Alzheimer's Disease Research Centers; the Nathan Shock Centers of Excellence in the Basic Biology of Aging; the Resource Centers for Minority Aging Research; the Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences of Aging; and the Centers on the Demography and Economics of Aging.

- *Pilot awards* are based on priorities identified in recent workshops. Projects involve multiple NIA-sponsored research centers to foster new and interdisciplinary collaborations.
- *Early career faculty education* includes seminars, lectures, webinars, and training programs. For example, training programs on grant writing and dementia palliative care are being offered in the summer/fall of 2022.
- *Web-based resource identification tools* enable users to locate publications, webinars, podcasts, and other materials.
- *Proposal development* will stimulate additional research to promote health and well-being among older Americans.

Evaluation Plans

NIH program staff review the progress of each OAIC every year as part of the noncompeting renewal process. In addition, annually each OAIC must convene an external advisory board of expert scientists from outside the OAIC institution(s) to evaluate progress and suggest any necessary changes in its scientific or administrative directions to achieve its stated goals. NIA may also conduct its own future independent evaluations of the OAIC program.

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 to discover new and effective ways to promote healthy and productive aging.

Table 2. Current Claude D. Pepper Older Americans Independence Centers

Institution and Location	Year Established
University of Michigan, Ann Arbor, MI	1989
Wake Forest University, Winston-Salem, NC	1991
Duke University, Durham, NC	1992[2094]
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994
The University of Texas Medical Branch, Galveston, TX	1999
Johns Hopkins University, Baltimore, MD	2003
University of Pittsburgh, Pittsburgh, PA	2004
University of Florida, Gainesville, FL	2007
Boston University, Boston, MA	2008
Mt. Sinai Medical Center, New York, NY	2010
University of California, San Francisco, CA	2013
The University of Texas Health Science Center, San Antonio, TX	2015
Northwestern University, Chicago, IL	2020
University of Connecticut, Farmington, CT	2021

[2094] A Center for the Study of Aging was started at Duke University in 1955; it was designated a Claude D. Pepper OAIC in 1992.

Paul D. Wellstone Muscular Dystrophy Specialized Research Centers

Establishment of the Paul D. Wellstone Muscular Dystrophy Specialized 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 (now Wellstone Muscular Dystrophy Specialized Research Centers, or Wellstone MDSRCs), 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 Wellstone MDSRCs Function Within the NIH Framework

Centers active in FY 2019–2021 are listed in Table 3. NIAMS, NICHD, and NINDS historically have funded up to six Wellstone MDSRCs. NHLBI has also co-sponsored competitions for Wellstone MDSRCs since 2007. NHLBI co-funds two centers and plans to support future MDSRC projects, contingent on the availability of funds and meritorious applications that align with NHLBI's mission.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles.[2095] 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 MDSRCs 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-chromosome-linked disease. The disease primarily affects males, because they carry only one X-chromosome, meaning that there is no chance for expression of a normal copy of the dystrophin gene (females have two X-chromosomes, one of which may be normal). Boys who have DMD do not produce dystrophin, which muscle cells need to function properly. DMD usually becomes evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their late 20s.[2096] Becker muscular dystrophy (BMD), 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.

[2095] https://www.ninds.nih.gov/health-information/disorders/muscular-dystrophy#:~:text=The%20muscular%20dystrophies%20(MD)%20are,until%20middle%20age%20or%20later
[2096] Broomfield J, et al. *Neurology* 2021:97(23): e2304. PMID: 34645707.

- *Facioscapulohumeral muscular dystrophy.* 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 that affect children, and others that 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.[2097]

Treatments such as physical therapy, the use of devices for support, corrective orthopaedic surgery, and drugs, can reduce symptoms and improve quality of life for some people who have muscular dystrophy. Some drugs, such as corticosteroids, can slow the progression of DMD to some extent but have adverse side effects. Several drugs have FDA approval to treat boys who have DMD, but their disease must be caused by specific gene variants for the treatments to be effective. A variety of other treatment strategies for muscular dystrophies, including gene and cell therapies, drugs, and biologics, are being developed and tested in animal and cell models. Clinical trials for some candidate therapeutics are underway, and a few trials have been completed. Due to the level of activity in the muscular dystrophy research field, clinical trial results and new drug applications are likely to continue to increase.

Burden of Illness

An estimated 1 of every 3,500–5,000 newborn males worldwide has DMD or BMD. Some 400–600 males in the U. S. are born with these dystrophies each year.[2098] Myotonic dystrophy affects approximately 1 in 8,000 people worldwide.[2099] FSHD affects approximately 1 in 20,000 people, and it affects men and women equally.[2100]

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDSRCs 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

[2097] Nallamilli BRR, et al. *Ann Clin Transl Neurol.* 2018;5(12):1574. PMID: 30564623.
[2098] National Library of Medicine, MedlinePlus. https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy
[2099] http://ghr.nlm.nih.gov/condition/myotonic-dystrophy
[2100] National Library of Medicine, MedlinePlus. https://ghr.nlm.nih.gov/condition/facioscapulohumeral-muscular-dystrophy

MDSRCs is to integrate activities, to develop therapies, and to apply other strategies to reduce the impact of muscular dystrophies on patients and their families.

Collectively, the Wellstone MDSRCs conduct research on various forms of muscular dystrophy, including some not listed above. Examples of research topics addressed by the Wellstone MDSRCs in FY 2019, FY 2020, and FY 2021 follow:

- At the University of Rochester MDSRC, 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. The center is funded through August 2023.
- The University of Iowa's MDSRC successfully competed for funding in FY 2020. Research at this MDSRC focuses on understanding the causes of and developing treatments for a group of dystrophies called dystroglycanopathies, which are associated with defects in muscle proteins known as dystroglycans. These diseases include some LGMDs and CMDs.
- Projects at the University of Florida MDSRC, which also include investigators from Northwestern University and UCLA, focus on the roles of inflammation, fibrosis, and fat infiltration in muscular dystrophy and on identifying strategies to counter these processes. This MDSRC successfully competed for funding in FY 2021.
- The Wellstone MDSRC at the University of Massachusetts continues to partner with investigators at Children's Hospital in Boston, the Kennedy Krieger Institute, and Children's Institute at Nationwide Children's Hospital, on studies of molecular, genetic, and epigenetic pathologies of FSHD, with the goal of developing potential therapies that can be tested clinically. This center is funded through May 2023.
- The MDSRC 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 Regional Medical Center at the University of Rochester. It focuses primarily on preclinical and clinical studies of DMD and FSHD and provides viral and plasmid vectors for studies in small- and large-animal models to investigators across the country. This center is funded through August 2023.
- Investigators at the University of Texas Southwestern Medical Center (UT Southwestern), the newest Wellstone MDSRC, 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. This center successfully competed for funding in FY 2020.

Each Wellstone MDSRC 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 2019, FY 2020, and FY 2021

NIH funding for the Wellstone MDSRC program was $8.9 million in FY 2019, $7.6 million in FY 2020, and $9.2 million in FY 2021.

FY 2019, FY 2020, and FY 2021 Progress Report

Programmatic Activities and Outcomes

Three Wellstone MDSRCs successfully competed for support in FY 2020 and FY 2021: the University of Iowa, University of Texas Southwestern, and University of Florida.

The Wellstone MDSRC program has also provided opportunities for public-private partnerships in muscular dystrophy. Productive collaborations between the MDSRCs and patient advocacy groups continue to promote patient participation, ensuring a patient voice in the conduct of research. For example, the Iowa MDSRC hosts an annual patient and family conference, during which researchers provide updates on scientific advances and patients provide data and biospecimens. The Rochester MDSRC hosts local myotonic dystrophy and FSHD patient meetings and sends a biannual newsletter to registry participants.

Several centers have industry collaborators. For example, the UT Southwestern MDSRC established the company Exonics Therapeutics to develop CRISPR-based therapeutics for DMD, and this company was acquired by Vertex Pharmaceuticals to continue to advance this treatment strategy.

All centers supported in FY 2019 have formal training and education cores. These facilities provided stipends to predoctoral and postdoctoral researchers, and they enhance the institutions' environments for training students, fellows, and early-stage investigators in muscular dystrophy research. The requirement for stipend support is being phased out beginning with the competing centers awarded in FY 2020 to better allow centers to provide additional training opportunities that can be leveraged by the entire muscular dystrophy scientific community.

The Wellstone MDSRC core facilities are national resources for the muscular dystrophy research community. These shared research tools foster collaborations across departments and schools within institutions, and among investigators and health care providers nationwide. Additional language was added to the FOAs for FY 2020 and FY 2021 competitions so that Data and Resource Sharing Plans are better defined regarding the processes for requesting and approving requests for core resources, and for improving the time between request and delivery. The FY 2020 and FY 2021 notice of awards included additional reporting requirements for each request of shared resources. Examples of shared core facilities include the following:

- The University of Rochester's National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy, which contains information about more than 2,400 patients, provides researchers with cell and tissue samples and clinical information about the donors of these samples. Since the beginning of FY 2019, the registry has facilitated 11 clinical studies and three patient events, and two additional clinical studies are currently under review, nearing approval.

- The University of Iowa Wellstone MDSRC 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 8,500 patients with various neuromuscular disorders. It also contains fibroblast cultures established from approximately 425 individuals, predominantly muscular dystrophy patients, which investigators will provide to other scientists upon request.
- The Resource and 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 MDSRC maintains a repository of tissues collected from FSHD patients and unaffected relatives, which has enabled statistically powered studies of biomarkers and candidate drugs. It provides both characterized FSHD cells and control muscle cells to laboratories that are studying FSHD or other muscular dystrophies. The center also provides animal models of FSHD to the research community as part of its core facilities.
- The University of Washington Wellstone MDSRC provides viral and plasmid vectors for studies involving the development and testing of potential therapies in small- and large-animal models. Services offered include consulting, reagents, and training related to vector production.
- The UT Southwestern Wellstone MDSRC provides a comprehensive electronic database that investigators can use to optimize exon-skipping strategies to rescue dystrophin expression in skeletal and cardiac muscle cells derived from iPSCs.

Research Activities and Outcomes

The Wellstone MDSRCs 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 MDSRC findings. Discoveries by investigators affiliated with the Wellstone MDSRC 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 2019, FY 2020, and FY 2021 include:

- The University of Rochester MDSRC has identified candidate serum biomarkers for FSHD using proteomics and DNA amplification approaches. In a study with 41 FSDH1 patients and 25 healthy controls, researchers validated nine conveniently assayable blood-based biomarkers that could be used to monitor FSHD disease activity and enable further therapeutic trials.[2101]
- The University of Iowa MDSRC has been studying muscular dystrophy in pregnancy and genetics. In one study, investigators enrolled women with LGMD type R9 (LGMDR9) in a natural history study, in which 22 participants completed a questionnaire about their pregnancy experiences. Of these, 13 participants reported 26 live births, 73 percent of which were uncomplicated and 96

[2101] Heier CR, et al. J Pers Med 2020;10(4):236. PMID: 33228131

percent of which involved no complications with infants. However, the share of pregnancies that required assisted vaginal labor and induction of labor were significantly larger than national averages, and nearly half of participants reported increased muscle weakness during pregnancy.[2102] Because one approach to treating DMD is to delete large portions of the defective dystrophin gene, which may impact the protein's stability, investigators tested the effects of such deletions on protein expression in heart and skeletal muscles and found that the shortened protein was long-lasting in vivo.[2103] Results from both studies referenced here were consistent with past findings but highlight the importance of continued robust research in these areas.

- Investigators at the University of Florida Wellstone MDSRC have advanced the development of therapeutic approaches for preserving and monitoring skeletal and cardiac muscle function in muscular dystrophy patients. A proof-of-concept study involved a high-throughput screening to identify compounds which correct the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling defect caused by a mutation in the Calpain 3 gene (CAPN3) that causes limb girdle muscular dystrophy type R1 (LGMDR1). Researchers identified the compound AMBMP and used a mouse model to demonstrate that it can reverse the LGMDR1 phenotype and restore exercise performance, thus supporting this approach for developing LGMDR1 therapies.[2104] A second study used MRI and magnetic resonance spectroscopy (MRS) biomarkers of leg muscles to quantify DMD disease progression. This prospective observational study involved 104 DMD patients and 51 healthy controls. Researchers found that corticosteroid treatment conveyed a 2.5-year delay in the average age at half-maximal muscle involvement in DMD.[2105] Another study aimed to elucidate the racial and ethnic make-up of the U.S. DMD population. From the identified observational studies, it was found that more than 70 percent of DMD study participants were White, less than five percent were Black or African American, and 3.3–26.5 percent were Hispanic or Latin American. These findings highlighted the need for effective recruitment, enrollment, and retention strategies for racially and ethnically diverse observational study populations.[2106]
- Researchers at the University of Massachusetts Wellstone MDSRC have demonstrated the use of RNAi-based small molecule therapy (a method using small pieces of RNA to interfere with the behavior of other molecules) to suppress the *DUX4* gene and thus potentially treat FSHD. In cell models of FSHD, this strategy inhibited *DUX4* and prevented *DUX4*-induced toxicity. In animal models, this RNAi gene therapy prevented muscle death.[2107] The researchers aim to continue identifying small molecules, namely micro-RNAs, that could be used as RNAi therapeutic vehicles to treat FSHD and other diseases.
- Researchers at the University of Washington Seattle Wellstone MDSRC developed a dystrophic double-knockout (dko) mouse model that progresses into late-stage heart failure in a disease process that parallels DMD cardiomyopathy in humans. Using this model, investigators found that

[2102] Libell EM, et al. Muscle Nerve 2021;63(6);812-817. PMID: 33501999

[2103] Angulski ABB, et al. Sci Rep 2020;10(1):10967. PMID: 32620803

[2104] Liu J, et al. Cell Rep Med 2020;1(17):100122. PMID: 33205074.

[2105] Rooney WD, et al. Neurology 2020;94(15):e1622-e1633. PMID: 32184340.

[2106] Barnard AM, et al. *J Neuromuscul Dis* 2020;7(2):167-173. PMID: 31929119.

[2107] Saad NF, et al. *Nat Commun* 2021;12(1):7128. PMID: 34880230.

adeno-associated virus (AAV)-micro-dystrophin gene therapy prevented declines in cardiac function and prohibited the onset of inflammation and fibrosis that lead to heart failure.[2108] Another study compared the persistence of dystrophin expression in a mouse model after both the administration of recombinant AAV6:CRISPR-Cas9-mediated multi-exon deletion/reframing therapy and the combination of this therapy co-delivered with AAV-micro-dystrophin (a conventional gene-therapy approach). The single therapy showed a persistence of dystrophin levels in cardiomyocytes but not skeletal muscle, whereas the combination therapy showed long-term persistence of gene-edited dystrophins. These results indicate that long-term DMD therapy using CRISPR-Cas9 is most impactful when co-administered with a complimentary approach such as AAV-micro-dystrophin.[2109] In another study, investigators are determining which regions of the dystrophin protein are most needed to improve patient health following gene therapy. This mouse study identified a micro-dystrophin that is compatible with AAV carrying capacity and can improve health in ways superior to some other micro-dystrophins tested in past clinical trials.[2110]

- The UT Southwestern Wellstone MDSRC has generated three new mouse models of DMD, each with either exon 42, 45, or 52 deletions in the dystrophin gene. Researchers optimized the approach to develop these models by identifying single guide RNAs (sgRNAs) that could restore dystrophin expression by removing the targeted exons. Intramuscular administration of sgRNA expressive adeno-associated virus serotype 9 (AAV9) efficiently restored dystrophin expression in mice. When validating this gene editing approach using human-induced pluripotent stem cell (iPSC)-derived cardiomyocytes bearing the same DMD mutations, researchers determined that it could be an effective therapy for an approximate 18 percent of DMD patients.[2111]

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDSRCs

Evaluation Plans

NIH released an evaluation report in January 2019.[2112] Although NIH had refined the Wellstone MDSRC program since the program's inception in FY 2003, a comprehensive review at this time was appropriate because of significant changes in the neuromuscular disease research landscape during the intervening 15 years. Recommendations on potential enhancements to the Wellstone Centers program, as well as aspects that should be continued, focused on five areas: research portfolio, center structure and implementation, community engagement, research resources, and training and career development.

Recommendations described in the evaluation working group's report were incorporated into the FY 2020 and FY 2021 FOAs and were reflected in the notice of awards, explicitly outlining information that must be included in annual progress reports. For example, the FOA was edited to clarify that research on any muscular dystrophy—not just those listed in previous funding opportunity announcements or in the *MD-Care Act*—is eligible for consideration under the Wellstone MDSRC program. Text encouraging clinical trial

[2108] Howard ZM, et al. *JCI Insight* 2021;6(7):e146511. PMID: 33651713.
[2109] Bengtsson NE, et al. *Mol Ther* 2021;29(3):1070-1085. PMID: 33160075.
[2110] Ramos JN, et al. Mol Ther 2019;27(3):623-635. PMID: 30718090.
[2111] Min Y, et al. *Mol Ther* 2020;28(9):2044-2055. PMID: 32892813.
[2112] https://www.wellstonemdcenters.nih.gov/sites/wellstone/files/WellstoneCenterEvalRptExecSumm-508.pdf

readiness, biomarker and clinical outcome assessment measure development and validation, and natural history studies was featured more prominently than in previous announcements.

As noted above, centers that successfully compete for FY 2020 funding were no longer required to provide stipends to predoctoral and postdoctoral fellows. Instead, in response to discussions with the Wellstone MDSRC evaluation working group, the centers are now expected to promote trainee support through individual fellowships or career development awards from public and private funding organizations, to organize research meetings for trainees across the network of Wellstone MDSRCs, and to organize training activities, such as courses or webinars for the overall muscular dystrophy research community. The centers also are encouraged to provide opportunities for non-clinical students and postdoctoral researchers to be exposed to clinical research. Centers' clinical research projects should involve medical students, clinical fellows, and residents.

Future Directions

NIH is committed to supporting up to six outstanding Wellstone MDSRCs. Based on its funding commitment to the existing centers, NIH has announced an open competition with the intent to fund up to three centers (for a total of up to six active centers) in FY 2022, pending the availability of funds and a sufficient number of highly meritorious applications.[2113] The new FOA will feature changes to the requirements for principal investigators and will place greater emphasis on recruitment of trainees from disadvantaged and underrepresented backgrounds.

Table 3. Active Senator Paul D. Wellstone MDSRCs, FY 2019–2021

Institution and Location	Years Funded
University of Rochester, Rochester, NY	2003–present
University of Iowa, Iowa City, IA	2005–present
University of Florida, Gainesville, FL	2005–present
University of Massachusetts, Worcester, and Children's Hospital, Boston, MA	2013–present
University of Washington and the Fred Hutchinson Cancer Research Center, Seattle, WA	2014–present
University of Texas Southwestern Medical Center, Dallas, TX	2015–present

National Institute on Minority Health and Health Disparities Centers of Excellence

Establishment of NIMHD Disparities Centers of Excellence

The Centers of Excellence (COEs) program supported by NIMHD is one of several programs that are central to NIH's scientific investment strategy, which seeks to improve minority health and, ultimately, eliminate health disparities. The *Minority Health and Health Disparities Research and Education Act of 2000* (P.L. 106-525) included provisions for the NIMHD's predecessor, the National Center on Minority Health and Health Disparities (NCMHD), to assist institutions in supporting programs of excellence in biomedical and behavioral research training for individuals who are members of minority health disparity populations

[2113] https://grants.nih.gov/grants/guide/rfa-files/RFA-AR-23-001.html

or other health disparity populations.[2114] The Congressionally mandated responsibilities of NCMHD were transferred to NIMHD with the enactment of the *Patient Protection and Affordable Care Act* (Public Law 106-548), which established the NIMHD.

Distinguishing minority health and health disparities provides a platform for research to advance and generate knowledge that can improve the health of racial and ethnic minority populations and can reduce health disparity conditions across populations. Minority health research is the scientific investigation of singular and combinations of attributes, characteristics, behaviors, biology, and societal and environmental factors that influence the health of racial and ethnic minority population(s), including within-group or ethnic sub-populations, with the goal of improving health and preventing disease.

Health disparities research is a multidisciplinary field of study devoted to gaining greater scientific knowledge about the influence of health determinants, understanding the role of mechanisms, and determining how this knowledge is translated into interventions to reduce or eliminate adverse health outcomes.

Minority health is defined as distinctive health characteristics and attributes of racial and/or ethnic minority populations who are socially disadvantaged due in part to being subject to racist or discriminatory acts, and who are underserved in health care. Minority health populations are classified by the Office of Management and Budget Directive 15 into the following racial and ethnic categories: American Indian and Alaska Native; Asian; Black or African American; Hispanic or Latino; and Native Hawaiian or Other Pacific Islander.[2115]

NIH defines a health disparity as a health difference that adversely affects disadvantaged populations in comparison with a reference population, based on one or more health outcomes. NIH-designated populations who experience health disparities include racial and ethnic minority groups, less-privileged socioeconomic status (SES) populations, residents of underserved rural areas, and sexual and gender minority populations.

Relevant health differences may manifest in the near term and in the longer term. Long-term outcomes of health disparity include higher incidence or prevalence of disease, as well as earlier onset or more aggressive progression of disease; premature or excessive mortality from specific health conditions; greater global burden of disease, such as "disability-adjusted life years," as indicated by population health measures; poorer health behaviors and clinical outcomes associated with disease; and worse self-reported outcome measures that reflect daily functioning, quality of life, or symptoms from specific conditions.

[2114] 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).

[2115] OMB (Office of Management and Budget). (1977). Statistical Policy Directive No. 15, Race and Ethnic Standards for Federal Statistics and Administrative Reporting. See HHS Office of Minority Health's Explanation of Data Standards for Race, Ethnicity, Sex, Primary Language, and Disability: https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=3&lvlid=54

The difficulty of improving these outcomes suggests the need for a focus on long-term outcomes in the following areas:

- *Risk to well-being:* unhealthy behaviors, such as smoking, stress, obesity, racism or discrimination, unhealthy environmental conditions, less education, disadvantaged SES, limited language proficiency, poor nutrition, greater number of incidents that affect health, including violence, accidents, and injury
- *Biological/epigenetic risk:* earlier age of disease onset, presence of predisposing gene variants, metabolic differences, susceptibility, faster disease progression, greater disease severity
- *Clinical event risks (that adversely impact health, including quality indicators of health services):* differential treatment results, poor physician-patient communication, differences in treatment offered, poor management of comorbidities, poor symptom management, adverse events caused by medications
- *Utilization-of-care risks:* 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 at home, emergency room visits, or end-of-life/palliative care

NIMHD COEs address health disparities through the following strategies:

- Conducting and supporting clinical, health services, population health, and behavioral research
- Promoting the training of a diverse research workforce.
- 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 that would address health disparities in priority diseases and conditions by conducting research, training a diverse scientific workforce, and engaging the community. The work of the COEs supports the implementation of several NIH/HHS plans including the *NIH Minority Health and Health Disparities Strategic Plan 2021-2025*, *HHS Action Plan to Reduce Racial and Ethnic Health Disparities*[2116] and the *National Prevention Strategy*.

Since 2002, when the NIMHD/NCMHD established the COE program, NIMHD has supported more than 110 COEs in approximately 39 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands (Table 4 provides the locations of COEs funded between FY 2019-2021).

Initially, the program used three different funding mechanisms: Resource-Related Centers (R24), Exploratory Centers (P20), and Comprehensive Centers (P60). Using these different funding mechanisms allowed NIMHD to support institutions with varying levels of biomedical research expertise and capacity. This approach also enabled NIMHD to support both geographically and culturally diverse institutions that

[2116] https://www.minorityhealth.hhs.gov/assets/pdf/hhs/HHS_Plan_complete.pdf

have long-standing partnerships with local and regional communities and organizations addressing health disparities.

In FY 2017, NIMHD released a new funding opportunity announcement to support the creation of NIMHD *Specialized Centers of Excellence (COEs) on Minority Health and Health Disparities*. Under this new name, the COE program continued to conduct multidisciplinary, multilevel research, and provide research opportunities for post-doctoral fellows, junior faculty, and other early-stage investigators. NIMHD invested $16,337,834 in FY 2019, $15,159,393 in FY 2020 and $18,302,095 in FY 2021 to fund the Specialized Centers of Excellence program.

The types of institutions funded directly by the NIMHD COE program or through partnerships with NIMHD COEs include research-intensive institutions, historically Black colleges and universities, and Hispanic-serving institutions. NIMHD COEs also have been successful in developing novel partnerships with different types of nonacademic institutions, such as community-based organizations, local departments of public health, and local school districts. These partnerships provide a means for nonacademic institutions to engage in research on improving minority health and eliminating health disparities.

Description of Disease or Condition

The research and other COE activities that NIMHD supports are not limited to or focused on a single disease, illness, or condition. The COE program also supports collaborative minority health and health disparities research to identify biological, behavioral, sociocultural, environmental, and health system factors that contribute to disparities. It also supports the development of evidence-based interventions to reduce and manage targeted health conditions, such as CVD, hypertension, stroke, cancer, diabetes, HIV/AIDS, severe mental disorders, youth suicide, substance use, osteoarthritis, and obesity, conditions that disproportionately affect racial and ethnic minority and other populations that experience health disparities. NIMHD solicitations for COEs encompass not only diseases or conditions that disproportionately affect populations experiencing disparities in health, but also factors that influence health. The thematic research foci of the currently funded COEs include multiple factors that affect populations who experience health disparities, such as trauma and violence, intergenerational transmission of racialized stress, health literacy, the role of social networks, access to health care, and resilience through the life course.

Burden of Illness

The diversity of the contemporary American population is one of the nation's greatest assets. However, the richness of this diversity is challenged by the disproportionate burden of disease and illness in populations that experience health disparities. Compelling evidence of the disparities affecting the U.S.' racial and ethnic minority, socioeconomically disadvantaged, and rural populations—include shorter life expectancies and higher rates of cancer, birth defects, developmental disorders, infant mortality, asthma, diabetes, obesity, CVD, and stroke. Populations that suffer from health disparities also bear a disproportionate burden of morbidity and mortality associated with HIV/AIDS, autoimmune diseases (such as lupus and scleroderma), poor oral health, sexually transmitted diseases, mental disorders, violence, and substance use.

Scope of NIH Activities: Research and Programmatic

Guided by the *NIMHD Minority Health and Health Disparities Research Framework*,[2117] the scope of activities conducted by NIMHD COEs is based on a thematic focus that identifies key factors relevant to understanding and promoting minority health and the elimination of health disparities. Successful COE applications reflect the NIMHD Research Framework by addressing the intersection of domains of influence (biological, behavioral, physical environment, sociocultural environment, and health care system) and levels of influence (individual, interpersonal, community, and societal). This broad scope provides considerable flexibility for COEs to design and implement the multi- and transdisciplinary strategies, studies, interventions, and activities that are needed to reduce and ultimately eliminate health disparities. The NIMHD COE program requires all COEs to establish certain cores:

- The Administrative Core for carrying out and overseeing administrative matters and functions
- The Investigator Development Core that requires pilot awards and research support for early-stage investigators, junior faculty, and postdoctoral fellows
- The Research Projects Core for conducting, coordinating, generating, and advancing research on minority health and health disparities comprising one to three observational or interventions studies
- The Community Engagement and Dissemination Core to facilitate equitable collaborative and sustainable relationships with the community and other stakeholders in research and dissemination of effective health information messages and research findings

NIH Funding for FY 2019, FY 2020, and FY 2021

During FY 2016 to FY 2017, NIMHD COEs transitioned to a new funding mechanism, the cooperative agreement U54. NIH funding for the NIMHD Specialized COE program was $16.3 million in FY 2019, $15.2 million in FY 2020, and $18.3 million in FY 2021.

FY 2019, FY 2020, and FY 2021 Progress Report

Programmatic Activities and Outcomes

Twelve NIMHD Specialized COEs were active in FY 2019, FY 2020, and FY 2021.

Research Activities and Outcomes

The NIMHD-funded COEs produced several research accomplishments during FY 2019 to FY 2021. Below are select examples:

- The relationship between racial discrimination and preterm labor, a key measure of maternal health is an understudied area in research. A study from the University of California San Francisco's Specialized COE examined the associations between preterm labor and direct and vicarious racial discrimination among African American women at three life stages: childhood, adolescence, and adulthood.[2118] Findings showed a 48 percent increase in the odds of preterm labor with each unit increase in adolescent direct racial discrimination. Each unit increase in

[2117] https://nimhd.nih.gov/about/overview/research-framework/

[2118] Daniels, Katie P et al. *Maternal and child health journal* vol. 24,11 (2020). PMID: 32920761.

childhood vicarious racial discrimination was associated with a 45 percent increase in the odds of preterm labor. The results reveal an association between life-stage racial discrimination and preterm labor risk among African American women, which underscores the need for further research to understand how direct and vicarious racial discrimination at different developmental periods impact racial disparities in birth outcomes.

Another study from New York University School of Medicine's Specialized COE, sought to understand the effect of acculturation among immigrants on the gut microbiome by characterizing differences in the gut microbiome between 863 residents in the U.S., including 448 U.S.-born African American or Black, Hispanic or Latino, and White individuals, and 369 foreign-born Hispanic or Latino, and Korean participants.[2119] There were differences in gut microbiome composition across groups, with the largest difference being between foreign-born Korean and U.S.-born White participants. Differences in sub-operational taxonomic unit abundance, which is a categorization of bacteria, between foreign-born and U.S.-born groups were distinct from differences between U.S.-born groups. Researchers concluded that U.S. nativity is a determinant of the gut microbiome, suggesting the value of further research to determine if acculturation-related microbiome alterations have consequences for immigrant health.

- The *Wealth and Obesity among U.S. Adults Entering Midlife* is a study from the University of Alabama at Birmingham's Specialized COE.[2120] The study examined the relationship between wealth and obesity among adults entering midlife and whether this relationship varies by sex, race, and measure of wealth. The analysis found a robust association between wealth and midlife obesity as well as heterogeneity in the wealth-obesity association across sex, race, and measure of wealth. Except for African American or Black men, net worth generally had a significant and inverse relationship with obesity. The net worth-obesity association was largest among women and was driven primarily by home value, in addition to savings and debt for Black women. The association between wealth and obesity was generally robust but also complex, depending on sex, race, and measure of wealth. Research that does not consider multiple components of wealth may overlook the importance of economic resources in shaping obesity rates in the U.S. population.
- Rural areas of the U.S. experience disproportionate CRC death compared with urban areas. The Specialized COE at Johns Hopkins University's Center for Health Disparities Solutions conducted a population-based study investigating differences in CRC survival between rural and urban men in Utah.[2121] The prognostic factors for survival found that differences in cancer stage and treatment were not apparent among rural and urban CRC patients. Rural men experienced lower CRC survival, while men in both rural and urban areas showed some association between CRC survival with race and cancer treatment.

[2119] Peters, Brandilyn A et al. *The ISME journal* vol. 14,7 (2020). PMID: 32210364.
[2120] Wolf JD, et.al. Obesity (Silver Spring). 2019 Dec;27(12):2067-2075. PMID: 31642209.
[2121] Rogers Charles R, et.al. Cancer Causes Control. 2020 Mar;31(3): 241-253. PMID: 32002718.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NIMHD COEs

Since the program's inception in 2002, NIMHD COEs have made progress toward improving minority health and reducing health disparities. However, much remains to be done in designing studies 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 multilevel, multidomain interventions that work. NIMHD and its COEs cannot and do not act alone. NIMHD has sought and continues to seek new partners and has encouraged each COE to establish partnerships with other NIH-funded centers and programs, other federal agencies, and other groups committed to eliminating health disparities. NIMHD will continue to pursue ongoing recommendations, including efforts to achieve the following goals:

- Increase the diversity of the scientific workforce, especially the number of biomedical, clinical, and population and behavioral scientists from racial and ethnic minorities and other health disparity populations. Focused efforts are particularly important to help increase the number of scientists and researchers who 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 succeed in securing research funding for programs to address health disparities, as well as to help increase the number of those who serve in leadership and decision-making roles as members of scientific review panels, members of national advisory councils, and as directors of research units within academic health centers.
- Create opportunities for biomedical and behavioral scientists to work with population scientists, health services researchers, and other public health researchers to address the transdisciplinary challenges more effectively in health disparities elimination and prevention research.
- Enhance the nation's capacity to conduct health disparities research by expanding research and training opportunities. Increase outreach, information dissemination, and public education regarding NIH research.

Evaluation Plans

NIMHD program staff evaluate the COEs' annual progress by examining each COE's published peer-reviewed articles and any additional NIH research funding that is obtained by investigators who are associated with the COE. Additional metrics may include books and book chapters published, conferences sponsored and presentations given on health disparities, community engagement activities, such as health fairs and other forums for disseminating health promotion materials, community participation in research and clinical trials, and research training and professional development opportunities provided to emerging scientists. This review determines each COE's progress toward meeting the aims and objectives of its grant and helps identify areas of concern that need to be addressed.

Future Directions

The NIMHD COE program will continue to intensify research efforts to improve minority health and understand, reduce, and eliminate health disparities, with an emphasis on sustaining current partnerships and establishing new ones. With the establishment of new partnerships, NIMHD expects that its COEs will continue to provide 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 specialized COEs will advance knowledge on social and cultural determinants of health through much-needed community-based interventions. Such community-based interventions will have a positive impact on the health status of underserved populations. It will also continue to be important to conduct population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the U.S., and NIMHD will continue to support studies to eliminate or decrease the impact of factors that contribute to the excess risks, morbidity, and mortality associated with living in some regions of the U.S.

The success of these and future research efforts by the NIMHD COEs will continue to depend, in part, on the development of improved methodological tools, measures, validated instruments, and novel research designs for teasing out the contribution of biologic, behavioral, and social factors in health disparities, as well as on identifying the role that health policies and practices play in reducing health disparities. The success of these COEs will also depend on collaboration with important partners—including community organizations, local government, and health care systems—to ensure that research findings have true community impact.

Table 4. NIMHD Centers of Excellence Active in FY 2019, 2020, and 2021

Institution	Title/ Center's Name	Project	Activity Code
University of Miami Coral Gables	Center for Latino Health Research Opportunities	MD002266-11	U54
University of New Mexico Health Sciences Center	Transdisciplinary Research, Equity and Engagement Center for Advancing Behavioral Health	MD004811-06	U54
University of Alabama at Birmingham	Obesity Health Disparities Research Center	MD000502-15	U54
Johns Hopkins University	Johns Hopkins Center for Health Disparities Solutions	MD000214-16	U54
Duke University	Duke Center for Research to Advance Healthcare Equity	MD012530-01	U54
University of Colorado Denver	American Indian and Alaska Native Health Disparities	MD000507-15	U54
Arizona State University-Tempe Campus	Leveraging Bio-Cultural Mechanisms to Maximize the Impact of Multi-Level Preventable Disease Interventions with Southwest Populations	MD002316-11	U54
University of Arkansas for Medical Sciences	Arkansas Center for Health Disparities: An NIMHD COE	MD002329-11	U54

Institution	Title/ Center's Name	Project	Activity Code
Case Western Reserve University	Involving Communities in Delivering and Disseminating Health Disparity Interventions	MD002265-11	U54
New York University School of Medicine	NYU Center for the Study of Asian American Health	MD000538-15	U54
University of North Texas Health Science Center	Texas Center for Minority Health, Education, Research and Outreach	MD006882-06	U54
University of Illinois at Chicago	Center for Health Equity Research	MD012523-01	U54

Rare Diseases Clinical Research

Establishment of the Rare Diseases Clinical Research Network

The *Rare Diseases Act of 2002* (P.L. 107-280) defines a rare disease as a condition affecting fewer than 200,000 individuals in the U.S. Collectively, an estimated 7,000 diseases or conditions fall into this category; cumulatively, approximately 25 to 30 million people in the U.S. have a rare disease. Thus, rare diseases are a significant public health concern, and given these statistics, rare diseases are not rare. Most of these disorders are serious or life-threatening and lead to significant morbidity and mortality.

Despite advances in our understanding of the causes and mechanisms of many diseases, effective treatments are available for only a small number of these conditions. FDA-approved treatments exist for approximately five percent of these conditions. Although the pace of rare disease therapeutics development has increased in recent years, addressing and resolving one disease at a time is an approach that takes too long when considering these diseases as a public health concern.

To help address the challenges of developing treatments for rare diseases, the *Rare Diseases Act of 2002* (P.L. 107-280) directed the Office of Rare Diseases Research (now the Division of Rare Disease Research Innovation) at NIH to "enter into cooperative agreements with or make grants for regional centers of excellence on rare diseases." These COEs were initiated in 2003 with the establishment of the Rare Diseases Clinical Research Network (RDCRN) and have been continually funded since that time.

How RDCRN Functions within the NIH Framework

The RDCRN is a collaborative effort that reaches across ten NIH ICOs: NCATS, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NINDS, NIMH, and ODS within the NIH Office of the Director. The network is supported through a cooperative agreement, meaning there is significant involvement by representatives from the participating NIH ICOs that provide funding to the network.

The RDCRN program is designed to advance research on rare diseases by promoting highly collaborative, multisite, patient-centric translational and clinical research. The structure of the RDCRN consists of multiple Rare Diseases Clinical Research Consortia (RDCRC) and a single Data Management and Coordinating Center (DMCC). Each individual consortium:

- Studies three or more rare diseases
- Consists of multiple sites
- Conducts three to five clinical research studies, with one being a natural history or longitudinal study
- Conducts pilot research studies to help drive the science
- Provides a career enhancement program for early-career investigators
- Fully integrates patient advocacy groups into its program
- Works collaboratively with the DMCC

The DMCC was established to facilitate and support the activities of each individual consortium, as well as cross-network activities. An important component of the RDCRN is the meaningful partnership each consortium is required to maintain with patients and patient advocacy groups (PAGs). The Coalition for Patient Advocacy Groups (CPAG) brings together the stakeholder organizations from all consortia within the RDCRN with the intent of sharing information and resources from across the network.

As of the end of 2021, the RDCRN has supported 31 consortia, with 20 of them currently active (see Table 5). Investigators report that the program has resulted in:

- Over 1,495 cumulative publications
- Over 2,437 cumulative presentations
- More than 300 early-stage investigators supported, including 186 MDs, 63 PhDs, 52 MD/PhDs, and seven with other degrees
- 76 cumulative studies leading to changes in practice
- 141 pilot studies

Through a competitive peer review process, the RDCRN grants are awarded every five years. In 2021, the Network is in its fourth award cycle (RDCRN.4) since inception. The competition for the fifth cycle (RDCRN.5) will be delayed by one year to allow RDCRN.4 investigators to complete work that was interrupted by pandemic shutdowns. RDCRN.5 grants will be awarded in FY 2025.

To learn more about the RDCRN consortia and the DMCC, visit the RDCRN website.[2122]

Description of Disease or Condition

For the purpose of the RDCRN, rare diseases may fall into one of the following categories:

- Disorders: physical or mental conditions or ailments
- Syndromes: group of symptoms that occur together, or a condition characterized by a set of associated symptoms
- Diseases: a disorder of structure or function that effects a specific location and is not simply a result of physical injury
- Manifestations: symptom or sign of an ailment

[2122] https://rdcrn.org/

- Conditions: a particular state of being that limits/restricts something else

Approximately 80 percent of rare diseases are believed to be of genetic origin. It is estimated that at least 50 percent of the patients are children.

Burden of Illness

The burden of illness for rare diseases is difficult to assess because of the large number of different disorders, the complexity of each disease, and the limited availability of prevalence and incidence data. Beyond the individual burden of a specific disorder, families, and patients with rare diseases face many of the same challenges including:

- Diagnosis: It can take years or even a decade to receive an accurate diagnosis. This is commonly referred to as the "diagnostic odyssey."
- Access to experts: There are often few physicians with expertise in any given rare disease, which might require that a patient travel great distances for consultations, treatments, or clinical trials.
- Treatment: There are often no treatments available for the patient. Only a limited number of pharmaceutical and biotech companies conduct research into rare diseases because it is difficult to recover the costs of developing treatments for small, geographically dispersed populations.
- Social/Emotional: Patients and families often feel alone and isolated in navigating the challenges that accompany diagnosis and treatment of rare diseases.
- Financial: Rare diseases represent a disproportionate share of health care spending. The numerous physician visits, tests, and expensive treatments—when they do exist—and the severity of the illnesses can be financially devastating for families.

Scope of NIH Activities: Research and Programmatic

RDCRN.4 consists of 20 consortia (Figure 62):

- 166 CPAG partners
- ~181 rare diseases being evaluated
- 358 clinical sites
- 12 countries
- Approximately 3,000 researchers and staff

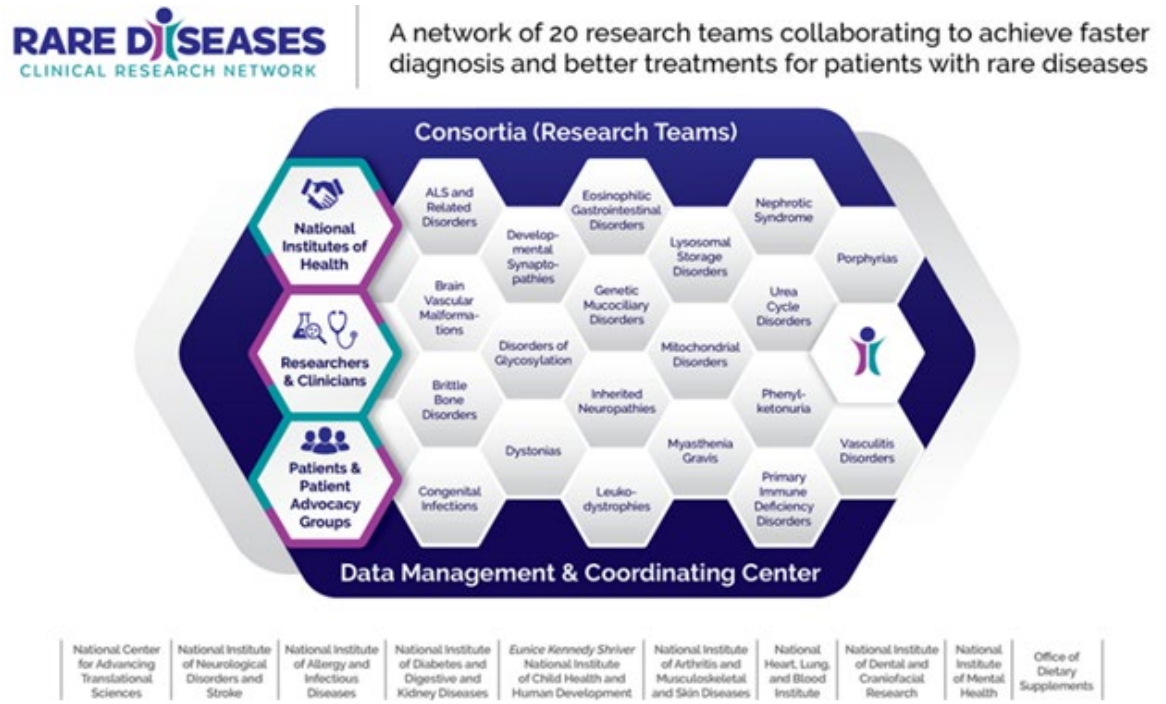


Figure 62: The Rare Disease Clinical Research Network

RDCRN

The RDCRN has made outstanding progress over the last 15 years, but it is important for initiatives to keep pace with changes in science, technology, and the requirements of regulatory agencies and funding sources, within the scope of developing treatments for rare diseases. Rare disease research often focuses on one disorder at a time, making progress extremely slow. An area of emphasis in the fourth cycle of the RDCRN is to collaborate to identify common threads, common mechanisms, and common solutions for common problems across all the consortia within the RDCRN.

Leadership of the RDCRN is managed by three committees. The first is the RDCRN Investigator Steering Committee, which consists of PIs from each consortium, PIs of the DMCC, two CPAG representatives, and NIH program staff. The second is the RDCRN CPAG Steering Committee, with representatives from one PAG from each consortium, representatives from the DMCC, two PI representatives, and NIH program staff. Each of these two steering committees is led by elected chairs. The chairs of both the Investigator and CPAG steering committees compose third group, the Joint Leadership Committee of the network, which provides oversight for cross-network activities.

RDCRN Consortia

The consortia in the RDCRN.4 cycle are intended to advance the diagnosis, management, and treatment of rare diseases with a focus on clinical trial readiness. Each consortium emphasizes highly collaborative, multisite, patient-centric, translational, and clinical research with the intent of addressing unmet clinical trial readiness needs, such as having validated clinical research tools and knowledge of disease natural history, which will move the field forward from its current state. Simply stated, the purpose of clinical trial readiness is to de-risk the drug development process by reducing the risks, time delays, and costs of

advancing basic research breakthroughs into treatments. Within the context of the RDCRN, the "de-risking" process is intended to begin early in the drug development pathway, parallel to basic and preclinical research. Examples of clinical trial readiness within the RDCRN includes studies that validate clinical research tools that have biomarkers or clinical outcome assessment measures that are fit-for-purpose within a defined context of use relevant to clinical trials. Studies also include projects that expand the knowledge of disease natural history necessary for clinical trial design; studies identifying characteristics for stratification or for determining inclusion and exclusion criteria; the stage of disease progression that may be responsive to treatment; and data needed to best determine sample size. It is important to emphasize that the science conducted within the RDCRN must adhere to NIH principles of rigor and reproducibility.

RDCRN DMCC

The mission of the DMCC is to provide clinical research and data management support to the individual consortia, coordinate activities across the RDCRN, and help to establish an identity for the network as a resource for research in rare diseases. It also serves as a conduit of information for both the research community and the public, as related to the rare diseases research being conducted within the network. The DMCC, which made significant organizational changes in RDCRN.4, provides services and resources to the network via four cores: Data Management Core, Clinical Management Core, Engagement and Dissemination Core, and Administrative Core.

The DMCC Data Management Core's responsibility is to support and enhance a collaborative informatics community for the RDCRN. The flexibility of the DMCC allows it to stay in alignment with NIH's new Data Management and Sharing Policy as it accomplishes three interrelated tasks. First, the DMCC must coordinate and support efforts to develop and monitor good data practices by promoting findable, accessible, interoperable, and reusable (FAIR) data principles of clinical and research data. It must also coordinate and facilitate data standards across the network. Lastly, it must encourage the use of CDEs. Significant efforts have also been made to have discussions with external groups (e.g., FDA, Clinical Data Interchange Standards Consortium, Critical Path Institute) to ensure that efforts related to data standards and management are interoperable with other initiatives within the rare diseases research community. Data standardization is an important focus in RDCRN.4. To achieve this, the DMCC is working closely with the consortia within the network to establish data standardization using common processes, tools, ontologies, and data elements upon acquisition. Tools such as REDCap have been introduced to streamline the data cleaning process to help ensure standardization and that data are formatted from the start of the data collection process.

The Clinical Research Core of the DMCC serves as a network resource, providing expertise and consulting with the consortia in protocol development and management, biostatistics, study designs and support in establishing single IRBs. Working as collaborative partners, the DMCC provides assistance and guidance where the investigators need support.

The purpose of the Engagement and Dissemination Core is to work collaboratively with the consortia and the PAGs to develop outreach plans for the network. The outreach is intended for basic and clinical researchers, academic and practicing physicians, patients, and the public.

The Administrative Core coordinates and supports all RDCRN-wide activities, including various committees and special interest groups (e.g., Joint Leadership Committee, Network Steering Committee, Strategic Planning Committee, Sustainability Special Interest Group, Diversity Special Interest Group, COVID Special Interest Group, Career Enhancement Committee).

RDCRN CPAG

Establishing effective interactions and collaborations with physicians, institutions, patient groups and drug developers has been found to be a successful model in bringing new treatments to market. Such a collaborative environment, epitomized by the partnerships between each consortium and its PAGs, has been at the heart of the achievements of the RDCRN. In RDRCN.4 the CPAG has a more formal role within the network. With the support of the DMCC, a steering committee was established consisting of one PAG representative from each consortium, representatives from the group of principle investigators, and NIH representatives.

The CPAG steering committee develops activities such as informational webinars that provide members with the tools needed to be informed and active partners, both within the individual consortium and across the RDCRN. The PAGs are also encouraged to share information and best practices across consortia. This allows for multiple PAGs in one consortium to work together and share resources. Members of the CPAG participate in network-wide working groups alongside RDCRN investigators. The CPAGs are also vital to development of a consortium's research studies and dissemination of findings. RDCRN investigators work closely with the PAG members and consistently involve their consortium patient groups in protocol development, such as the development of survey questions or clinical trial design. PAGs are also the primary source of dissemination or sharing of research protocols for recruitment for their patient communities.

NIH Funding for FY 2019, FY 2020, and FY 2021

The RDCRN is made possible through awards by NIH, totaling roughly $33 million in FY 2021 funding alone, with an average of $1.46 million per consortium per FY.

The RDCRN investigators have been able to take advantage of the ripple effect produced by NIH funding. Across the entire course of the RDCRN, associated investigators have leveraged the existing network infrastructure to expand their rare disease research programs through the receipt of 112 additional NIH rare disease research grants. NIH funding has also attracted the support of CPAGs, industry, angel investors, non-federal grants, and institutional support.

FY 2019, FY 2020, and FY 2021 Progress Report

Programmatic Activities and Outcomes

Examples of some RDCRN programmatic activities and outcomes in FY 2019, 2020, and 2021.

- The RDCRN, like the rest of the world, was significantly affected by the pandemic. The RDCRN investigators and CPAG collaborated to conduct a survey investigating the impacts of the pandemic on the rare disease community, including physical and emotional health, the availability of supplies, access to care, and other challenges. The study was launched in May 2020 and ran

through December of the same year. Approximately 3,400 individuals from across the U. S. participated, representing 130 distinct rare diseases.

Preliminary results indicated that the pandemic negatively affected rare disease patients and their caregivers in terms of access to regular health care, treatment for the rare disease, special diet, and special treatment and hospitalization. Some respondents had difficulty receiving treatments, especially those requiring special diets, occupational therapies, and physical therapies. The pandemic also caused mood changes, anxiety, and stress, in both the patients and their family members to an extent that required medical attention. A follow-up survey focused on vaccine hesitancy and uptake, along with the longer-term impact of the vaccination on the rare disease community was underway in 2021. Information and preliminary results are available on the RDCRN webpage.[2123]

- An important role of the NIH is the stewardship and long-term care of the valuable resources that are produced from rare disease research. A primary role of the DMCC is to ensure that all types of data can be stored and are accessible to appropriate stakeholders. The DMCC Data Management Core provides a cloud computing platform and engineering support that is provisioned by the Information Resources Technology Branch (ITRB) of NCATS. The NCATS ITRB worked together with the DMCC to provide two cloud-based, secure data environments to support data collection and storage, as illustrated in Figure 63.

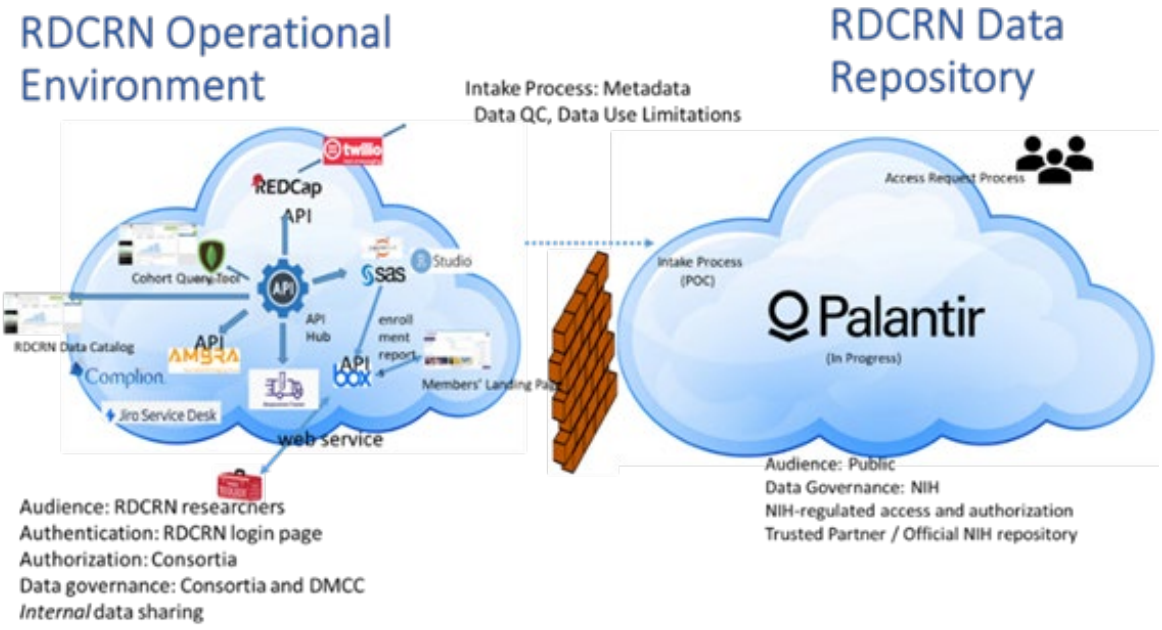


Figure 63: The RDCRN Operational Environment and RDCRN-Data Repository

- Newly established for RDCRN.4, the RDCRN operational environment enables consortia to store personally identifiable information (PII) in a system that is compliant with the regulations as

[2123] Preliminary Survey Results Highlight Impact of COVID-19 on Rare Disease Community. February 10, 2021. https://www.rarediseasesnetwork.org/news/2021-02-10-COVID19-survey-preliminary-results

outlined by the 1996 *Health Insurance Portability and Accountability Act* (HIPAA) and IRB, with a database that can be expanded to include various types of data, both structured (tabular) and unstructured (images, documents etc.) This allows the consortia, working within the operational environment, to have access to all consortium-specific data in one location, which streamlines the data access and identification process involved in data storage. Standard tools for intake and organization of data are available as well, allowing users to store image, video, and genomics data types. The DMCC and NCATS have worked diligently to turn various components into a data ecosystem where data is collected and analyzed in a single secure environment.

- The DMCC, in collaboration with NCATS, is establishing a dedicated NCATS RDCRN data warehouse (RDCRN-DW). The RDCRN-DW is an NIH data-sharing resource that will contain clinical research data from individuals with rare diseases who are enrolled in an RDCRN-sponsored protocol. A variety of data modalities will be contained in the RDCRN-DW, including natural history, imaging, genomic, actigraphy and other data from individuals. Rare disease research is often hampered by the small size of the study population, so the purpose of this data warehouse is to enable secondary analyses of existing, harmonized research data from clinical studies and trials. Data in the RDCRN-DW is harmonized to published data standards, where feasible, to facilitate meta-analyses and merging with additional data sets. The data warehouse will be a highly interoperable, secure, clinical data research environment that will harmonize clinical and patient data. The NCATS RDCRN-DW is being created by NCATS as part of the government response to centralize the collection and enable secondary analysis of diverse rare disease research data sets. NCATS intends to provide access to the data for use by researchers for public health purposes and decision making, including conducting and supporting research to define the clinical natural history of rare diseases, assessing therapeutic responses and outcomes, and conducting and supporting a broad range of studies.

Research Activities and Outcomes

Examples of some RDCRN research activities and outcomes in FY 2019, 2020, and 2021 are outlined below.

- Gaining a better understanding of biological components that play a role in a rare disease is key to developing an effective treatment. In order to better understand eosinophilic gastrointestinal disorders, a group of disorders characterized by pathologic eosinophilic infiltration of the esophagus, stomach, small intestine, or colon, the Consortium of Eosinophilic Gastrointestinal Disease Researchers is focused on the eosinophil, a type of disease-fighting white blood cell, which has emerged as an exciting component of the immune system. Much of the past eosinophil research has been conducted in mice and has only recently moved to humans. The research team published *Eosinophil Knockout Humans: Uncovering the Role of Eosinophils Through Eosinophil-Directed Biological Therapies,* a review article synthesizing the current data on eosinophils in health and disease. [2124] Basic animal research has pointed to the role of eosinophils in basal and inflammatory processes and in protective immunity. Recently, a series of anti-eosinophil therapeutics have emerged as a new class of drugs that dramatically deplete eosinophils and

[2124] Jacobsen EA, et al. *Annu Rev Immunol* 2021;39:719-757. PMID: 33646859.

provide a valuable opportunity to see the consequences of eosinophil depletion in humans and compare the impact of depleted eosinophils on humans and in mice. Initial results demonstrate that in humans eosinophils negatively contribute to a variety of diseases and, unlike mouse eosinophils, do not yet have an identified role in physiological health. This is an important step in better understanding the role of eosinophils in humans, and it can provide important information related to the development of treatments.

- The identification of biomarkers is an extremely important part of clinical trial readiness. They can serve a prognostic role and can indicate whether a treatment has reached its target in clinical trials. The Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium (CReATe) sought to identify a powerful biomarker for ALS) and validated that serum neurofilament light (NfL) may be a prognostic biomarker for ALS. They published the *Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS* in 2020.[2125] The research team set out to identify the preferred neurofilament assays and clinically validate serum neurofilament light (NfL) and phosphorylated neurofilament heavy (pNfH) as both a prognostic and pharmacodynamic biomarker relevant to the development of therapies for ALS. Investigators used serum and cerebrospinal fluid from a large group of patients with ALS and related disorders who had undergone careful longitudinal clinical phenotyping, along with a serial collection of biological samples. Serum NfL (and perhaps pNfH), quantified using the specific assays, has potential utility as a pharmacodynamic biomarker of treatment effect. These results will help identify whether drugs in treatment trials are effective.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of RDCRN

Future Directions

The continued commitment of NCATS and other NIH ICOs is a testament to the effectiveness of the principles of the RDCRN. Many of the RDCRN's novel practices have been adopted, and the network's impact on the rare diseases community and rare disease research is immense.

The fifth round of applications to the RDCRN consortia and the DMCC (RDCRN.5) will be awarded in 2025. The focus of the upcoming cycle will continue to be on clinical trial readiness, that is, addressing unmet needs that will move the research forward from its current state in a rigorous and swift manner toward trials and, ultimately, treatment.

RDCRN.5 will also embrace NCATS' approach to translational science, which emphasizes recognition of the commonalities across diseases, including rare diseases. By identifying shared molecular biology, signaling pathways, and other common characteristics across several diseases at one time, researchers hope that results can be informative for multiple disorders simultaneously. This is one approach the NCATS is taking to transform how research is conducted, to speed the translation of discoveries in the laboratory to therapeutics in the clinic.

[2125] Benatar M, et al. *Neurology* 2020;95(1):e59-e69. PMID: 32385188.

In addition, RDCRN.5 will focus on using the NIH inclusion policies for research involving human subjects to plan enrollment for rare disease research studies that will help promote expanded outreach to diverse populations. In examining the clinical enrollment of 22 RDCRN natural history studies, conducted between 2014 and 2021, it was found that 23 percent of the researchers based their targeted enrollment on known genetic disposition. More often—41 percent of the time—the targeted enrollment of the study was based on existing registry data, a prior study population, or current clinic patients. Furthermore, 36 percent of investigators based their targeted enrollment on U.S. demographic data. The mean enrollment of Black individuals across all studies was 4.3 percent (range 0–26 percent), compared with the mean planned enrollment of 8.2 percent. For Hispanic individuals, the mean enrollment was 11.8 percent (range 1–46 percent), compared with the planned enrollment of 13.9 percent. The RDCRN will continue to develop community outreach through the RDCRN diversity special interest group, the CPAGs, and various diversity activities within individual consortia. It will also continue outreach to various community programs, such as the Rare Disease Diversity Coalition, to explore methods of expanding research into different communities.

The DMCC will embrace the NIH Strategic Plan for Data Science,[2126] with an emphasis on FAIR data principles and a move toward common architecture, infrastructure, and tools to establish a platform for building resources for investigators and the research community to share.

Evaluation Plans

Program staff from ICOs that support the RDCRN meet monthly to discuss its progress. The program has taken an agile approach to RDCRN management. By meeting and discussing the status of the program regularly and suggesting improvements and process optimization when needed, issues are often managed before they become problems. The program will continue to be evaluate by data-driven metrics, and NIH programmatic oversite.

Table 5. All funded RDCRN consortia

Consortium Name	RDCRN.1 2003-2008	RDCRN.2 2009-2013	RDCRN.3 2014-2018	RDCRN.4 2019-2024
Genetic Disorders of Mucociliary Clearance Consortium	X	X	X	X
Urea Cycle Disorders Consortium	X	X	X	X
Vasculitis Clinical Research Consortium	X	X	X	X
Porphyrias Consortium		X	X	X
North American Mitochondrial Disease Consortium		X	X	X
Dystonia Coalition		X	X	X
Brain Vascular Malformation Consortium		X	X	X
Nephrotic Syndrome Study Network		X	X	X

[2126] Final NIH Policy for Data Management and Sharing. NOT-OD-21-013. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html

Consortium Name	RDCRN.1 2003-2008	RDCRN.2 2009-2013	RDCRN.3 2014-2018	RDCRN.4 2019-2024
Primary Immune Deficiency Treatment Consortium		X	X	X
Inherited Neuropathy Consortium		X	X	X
Lysosomal Disease Network		X	X	X
Clinical Research in ALS and Related Disorders for Therapeutic Development			X	X
Brittle Bone Disorders Consortium			X	X
Consortium of Eosinophilic Gastrointestinal Disease Researchers			X	X
Developmental Synaptopathies Consortium			X	X
Phenylalanine Families and Researchers Exploring Evidence				X
Myasthenia Gravis Rare Disease Network				X
Congenital and Perinatal Infections Consortium				X
Frontiers in Congenital Disorders of Glycosylation				X
Global Leukodystrophy Initiative Clinical Trials Network				X
Rett Syndrome, MECP2 Duplications, and Rett-related Disorders Consortium	X	X	X	
Rare Kidney Stone Consortium		X	X	
Sterol and Isoprenoid Diseases Consortium		X	X	
Autonomic Disorders Consortium		X	X	
Rare Lung Diseases Consortium	X		X	
Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium			X	
Clinical Investigation of Neurologic Channelopathies	X	X		
Salivary Gland Carcinomas Consortium		X		
Chronic Graft Versus Host Disease Consortium		X		
Bone Marrow Failure Consortium	X			
Rare Genetic Steroid Disorders Consortium	X			
Rare Thrombotic Diseases Consortium	X			
Cholestatic Liver Disease Consortium	X			
Data Management and Coordinating Center-CCHMC				X
Data Management and Coordinating Center-USF	X	X	X	

Autism Centers of Excellence

Establishment of the Autism Centers of Excellence

According to CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, nearly 1 in 44 8-year-old children have ASD.[2127] These estimates are based on data collected from health and special education records of children living in 11 areas of the U.S. during 2018. NIH is working to better understand the causes of ASD and to develop treatments for ASD, which can, at times, be serious and disabling.

To expand the public health response to the challenges posed by ASD, Congress passed the *Combating Autism Act of 2006*, which was aimed at expanding research and improving coordination among public health research agencies, including NIH. The *Combating Autism Act* reauthorized the IACC, a federal advisory committee designed to coordinate agency activities and identify priority areas in an annual Strategic Plan for ASD Research. As part of its response to the *Combating Autism Act*, NIH formed the ACE program by consolidating two previous ASD research programs, the Collaborative Programs of Excellence in Autism (established in 1997) and Studies to Advance Autism Research and Treatment (established in 2002 and completed in 2008), into a single research effort.

Congress reauthorized these federal ASD activities (including the ACE program and the IACC) through the *Autism Collaboration, Accountability, Research, Education, and Support Act of 2019* (the *Autism CARES Act*, P.L. 116–60), which was signed into law September 2019. The *Autism CARES Act of 2019* includes new provisions to expand the focus of government activities to include the entire lifespan of people on the autism spectrum. In addition, the Act requires a report to Congress on health and well-being. The *Autism CARES Act* expires September 2024.

How the Autism Centers of Excellence Function Within the NIH Framework

The goals of the ACE program were established by the NIH Autism Coordinating Committee (ACC), a working group composed of representatives from NIH Institutes that support the largest share of NIH's ASD research. The ACC is tasked with enhancing the quality, pace, and coordination of research efforts at NIH and monitoring scientific progress on an ongoing basis. The five current ACC member Institutes (NICHD, NIDCD, NIEHS, NIMH, and NINDS) provide funding to the ACE program and share administrative and oversight responsibilities.

The ACE program, which is informed by the Strategic Plan for ASD developed and updated by the IACC, serves as a flagship initiative for NIH's autism research portfolio. ACE grants enable large-scale center and network projects that could not be supported through a typical NIH grant.

The initial ACE program, funding for which began in FY 2007 and FY 2008, focused on identifying the causes of ASD and developing new and improved treatments. The second iteration of the ACE program, launched in FY 2012, focused on possible causes of ASD, risk and resilience in ASD, children with ASD who have limited speech and communication, preventive interventions and improved treatment, ASD among girls and women, and how genetic and environmental factors are associated with the development of ASD. In

[2127] Maenner, M, et al. *MMWR Surveill Summ* 2021;December 3;70(11);1-16.

2017, the ACE program began its third and current funding cycle. Research plan priority areas addressed through this current ACE program funding cycle include research on biomarkers, genetic susceptibility, pharmacological treatments, early intervention, and risk and protective factors.

The ACE program comprises both research 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, and each center conducts interdependent subprojects. ACE networks unite researchers at different facilities throughout the country, and working as a unit, each network addresses a particular research question in depth. NIH currently funds five ACE research center grants and five ACE research network grants (see Table 6).

Description of Disease or Condition

Leo Kanner first described autism in 1943 as a disorder "characterized by extreme aloneness and a desire for the preservation of sameness, with a variety of behavioral (cognitive, affective) symptoms derived from them."[2128] 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. Starting in infancy, a child 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

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 44 8-year-old children has ASD. Boys are approximately four times as likely as girls to have ASD.[2129] 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, or earlier and more accurate ASD diagnoses, or whether it can be attributed to increases in biologic, environmental, or other risk factors. A similar increase in ASD prevalence has occurred in other countries.

Although ASD can vary 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

[2128] Kanner L. *Nerv Child.* 1943;2:217-50.
[2129] https://www.cdc.gov/mmwr/volumes/70/ss/ss7011a1.htm

affected individuals. People with ASD may receive private and public services in special education settings, hospitals, university medical centers, or residential treatment facilities, among other settings.

The socioeconomic impact of ASD for families and society at large is tremendous. Scientists and economists have estimated that the annual cost of providing care for all Americans with ASD is between $34 billion and $236 billion.[2130,2131] The estimated costs over a lifetime for each person can total $1.4 million to $3 million.[2132,2133] Families often incur large debts for medical and education services that public programs or medical insurance do not cover. In addition, ASD often leads to profound emotional hardships for affected individuals and their families.

Scope of NIH Activities: Research and Programmatic

The centers and networks that make up the ACE program cover a broad range of ASD research areas, including early brain development and functioning, social interactions in infants, rare genetic variants and mutations, associations between autism-related genes and physical traits, underrepresented populations with ASD (such as women and girls and African Americans), and potential new treatments.

To support and accelerate research in the causes, diagnosis, and treatment of ASD, NIH created the National Database for Autism Research (NDAR), an informatics system and central repository for data from people with ASD. Beginning in 2020, data that were previously stored in NDAR are now incorporated in the NIMH Data Archive (NDA). NDA includes a wide range of human-subjects data, including phenotypic, clinical, and genomic data, as well as de-identified medical images, from individuals who participate in research, regardless of the source of research funding. NDA provides the infrastructure to store, search across, retrieve, and analyze these varied types of data. Although NDA receives data from many publicly and privately funded research sources, all ACE centers and networks are expected to contribute their data to NDA.

NIH Funding for FY 2019, FY 2020, and FY 2021

Five NIH Institutes fund the ACE program: NICHD, NIDCD, NIEHS, NIMH, and NINDS. NIH funding for the ACE program, which currently includes five research centers and five research networks, was $22.56 million in FY 2019, $22.90 million in FY 2020, and $22.38 million in FY 2021.[2134]

FY 2019, FY 2020, and FY 2021 Progress Report

Programmatic and Research Activities and Outcomes

The centers and networks that make up the ACE program cover a broad range of ASD research areas, including early brain development and functioning, social interactions in infants, rare genetic variants and mutations, associations between autism-related genes and physical traits, possible environmental risk

[2130] Ganz ML. *Arch Pediatr Adolesc Med.* 2007;161(4):343-9. PMID: 17404130.
[2131] Buescher AV, et al. *JAMA Pediatr* 2014;168(8):721-8. PMID: 24911948.
[2132] Ganz ML. *Arch Pediatr Adolesc Med* 2007;161(4):343-9. PMID: 17404130.
[2133] Buescher AV, et al. *JAMA Pediatr* 2014;168(8):721-8. PMID: 24911948.
[2134] NIH RePORT, accessed June 15, 2022. https://report.nih.gov/

factors and biomarkers, minimally verbal children, underrepresented populations with ASD (such as women and girls and African Americans), and potential new treatments.

The activities and accomplishments of the ACE program, including those centers and networks that received support in the first round of funding (FY 2007 and 2008), those that were funded in the second round (FY 2012), and those that were awarded in the third round (FY 2017), are noted in Table 6 and are highlighted briefly below.

Table 6. Autism Centers of Excellence (ACEs)

Institution and Location	Year Started		
	First Round	Second Round	Third Round
University of California, Davis, CA (1)	2007	—	—
University of California, Davis, CA (2)	—	2013	—
University of California, Davis, CA (3)	—	—	2017
University of California, Los Angeles, CA (1)	2007	2012	2017
University of California, Los Angeles, CA (2)	2008	2013	2018
University of California, Los Angeles, CA (3)	—	2012	—
University of California, San Diego, CA	2007	—	—
University of Illinois, Chicago, IL	2007	—	—
The University of North Carolina, Chapel Hill, NC (1)	2007	2012	2017
The University of North Carolina, Chapel Hill, NC (2)	—	2012	—
University of Pittsburgh, Pittsburgh, PA	2007	—	—
University of Washington, Seattle, WA	2007	—	—
Yale University, New Haven, CT	2008	2012	2017
Wayne State University, Detroit, MI	2008	—	—
Drexel University, Philadelphia, PA	2008	—	2017
Boston University, Boston, MA	—	2012	—
Emory University, Atlanta, GA	—	2012	2017
Boston Children's Hospital/Harvard Medical School, Boston, MA	—	2012	—
Mount Sinai School of Medicine, New York City, NY	—	2012	—
Duke University, Durham, NC	—	—	2017
The George Washington University, Washington, DC	—	—	2017*
Florida State University, Tallahassee, FL	—	—	2017
The University of Virginia, Charlottesville, VA	—	—	2018*

*Funding for the R01MH100028 ACE network was transferred from George Washington University, Washington, DC, to University of Virginia, Charlottesville, VA, in 2018 when the PI moved institutions.

ACE Centers and Networks Active During FY 2019–2021

- UCLA (*P50HD055784, 2007–2022):* For more than a decade, researchers at this UCLA-based ACE center have made significant advances in the field, identifying risk genes, candidate brain-based biomarkers of treatment response, and early risk markers of ASD beginning in the first few weeks of life. They developed new interventions for toddlers with social communication delays, identified a promising intervention to address repetitive behaviors, and showed how symptoms of ASD may be affected by connections between the thalamus (a part of the brain that generally regulates input from the senses to different parts of the brain) and the amygdala, which helps to process emotions.[2135] These scientists continue to work to determine how differences in genetic risk for autism affect early brain development, neuroimaging, and EEG biomarkers in the first year of life, to examine heterogeneity in treatment response using an adaptive treatment intervention for very young children at risk for ASD, to use MRI in youth with ASD to determine how behavioral differences and genetic risk differentially affect brain activation and structural and functional connectivity, and to conduct an early-stage pharmacological study aimed to increase social interest and social reward responsivity in adolescents and young adults enrolled in a social skills intervention.
- UCLA *(R01MH081754, 2008–2013; R01MH100027, 2013–2023):* Researchers in this UCLA-based ACE network have been utilizing large genomic databases to investigate how rare genetic variations, mutations, and abnormalities affect an individual's risk for autism. Their findings show that while common variations in genetic mutation at the individual level contribute less to a person's risk for autism,[2136] common inherited variants or mutations at the family level exert stronger effects on ASD risk.[2137] These researchers also reported that in families with multiple affected individuals, a substantial contribution to ASD risk comes from inherited rare variations.[2138] These ACE scientists have recruited a large number of research subjects with self-reported African ancestry (African Americans), an important population that has not previously been well represented in ASD genetic research. The researchers also identified several likely rare mutations in their African American cohort, including in known ASD risk genes, and found that existing measurements of risk for ASD derived from European populations perform poorly when applied to the African American cohort. In the current funding cycle, these scientists aim to increase the size of this cohort.[2139]
- The University of North Carolina at Chapel Hill *(R01HD055741, 2007–2022):* Researchers from this ACE network are studying abnormal processes in early brain development by examining images of the brains of very young children who are at risk for developing ASD because they have an older sibling with autism. Through this body of work, researchers have developed potential strategies for early identification (i.e., within the first year of life) of children at risk for developing ASD. An early study from this network found evidence of enlarged portions of the amygdala in 6- to 7-year-old children with ASD and showed that these differences were associated with deficits in

[2135] Green SA, et al. *Autism Res* 2017;10(5):801-9. PMID 27896947.
[2136] Anney R, et al. *Hum Mol Genet* 2012;21(21):4781-92. PMID: 22843504.
[2137] Gaugler T, et al. *Nat Genet* 2014;46(8):881-5. PMID: 25038753.
[2138] Leppa VM, et al. *Am J Hum Genet* 2016;99(3):540 PMID: 27569545.
[2139] Constantino JN, et al. *Pediatrics*. 2020;146(3). PMID: 32839243.

social and communicative behavior.[2140] More recently, these researchers identified that this accelerated amygdala growth occurs between 6 and 12 months of age, the period during which autistic behaviors first emerge.[2141] They also found that children who were diagnosed with ASD at 24 months had differences in the visual processing areas of the brain that were apparent at six months of age.[2142] Other work from this group showed early overall brain overgrowth in at-risk infants, and demonstrated that a computer algorithm that analyzed this brain growth identified a majority of infants who later developed autism.[2143] These researchers also found that among children at-risk for developing ASD, those who experienced sleep difficulties between 6 and 12 months of age were more likely to be diagnosed with ASD at 24 months of age. This may give clinicians another tool to identify early in development children at risk for autism and may provide insight into the potential role of sleep problems in the development of ASD.[2144]

- The University of Virginia *(R01MH100028, 2012–2022):* This ACE network is investigating ASD in women and girls, because this population is underexamined and evidence gaps exist in sex and gender differences and autism. The project will study a larger sample of girls with autism than has been studied previously, focusing on genes, brain function, and behavior throughout childhood, adolescence, and early adulthood. The objective is twofold: to identify the causes of ASD and to develop new treatments. By following children through adolescence and into adulthood, and with the contribution of a dataset of boys and girls with autism and their healthy brothers and sisters, the scientists aim to identify differences between boys and girls related to ASD risk and how they respond to interventions. The researchers also aim to uncover information that will help males and females living with ASD better manage the transition to adulthood.[2145, 2146]
- Emory University *(P50MH100029, 2012–2022):* The team of researchers at the Emory ACE center is studying risk and resilience in ASD, with particular interest in factors that lead to positive outcomes or social disability. The team is also conducting randomized clinical trials to develop treatments for 12-month-old children. The center will follow hundreds of infants from birth to 30 months, including those at high risk for ASD. Previously, this group demonstrated that, when looking at videos of people speaking, infants who were later diagnosed with ASD had eye movements that differed from those of typically developing infants.[2147] The group also found a genetic basis for those eye movements.[2148] Other recent findings showed an association between visual engagement and language acquisition in typically developing toddlers and toddlers with ASD who had acquired first words, but not in toddlers with ASD who were not yet verbal.[2149]
- Florida State University *(R01HD093055, 2017–2022):* Researchers in the Florida State University-based ACE network are testing a two-part intervention designed to empower parents of children

[2140] Kim JE, et al. *Arch Gen Psychiatry* 2010;67(11):1187-97. PMID: 21041620.
[2141] Shen, MD, et al. *Am J Psychiatry* 2022. PMID: 35331012.
[2142] Girault JB, et al. *Am J Psychiatry* 2022. PMID: 35615814.
[2143] Hazlett HC, et al. *Nature* 2017;542(7641):348-51. PMID: 28202961.
[2144] MacDuffie KE, et al. *Am J Psychiatry* 2020;177(6):518-525. PMID: 32375538.
[2145] Lawrence KE, et al. *Brain*. 2022 Mar 29;145(1):378-387. PMID: 34050743.
[2146] Harrop C, et al. *Autism Res*. 2021 Jan;14(1):156-168. PMID: 33274604.
[2147] Jones W, Klin A. *Nature* 2013;504(7480):427-31. PMID: 24196715.
[2148] Constantino JN, et al. *Nature* 2017;547(7663):340-4. PMID: 28700580.
[2149] Habayeb S, et al. *J Autism Dev Disord*. 2021 Jul;51(7):2519-2530. PMID: 33009972.

with ASD. The researchers are offering parents problem-solving education in a six-session intervention to help them access the services their children need and to adapt to caring for a child with special needs. Parents also receive training in early social interaction, which teaches them to support their children's communication and social skills in everyday routines, activities, and settings.

- Duke University *(P50HD093074, 2017–2022):* An estimated 40 to 60 percent of people with ASD have ADHD, which encompasses such symptoms as difficulty paying attention, problems controlling behavior, and hyperactivity. Scientists at the Duke University ACE center are examining how ADHD may influence the diagnosis and treatment of autism by observing children who have ASD alone, ASD and ADHD, and ADHD alone and comparing them with typically developing children. They are testing whether the stimulant medication used to treat ADHD will help children with both conditions.

  This group has also demonstrated that automated computer analysis can detect atypical behaviors in toddlers with ASD. They have developed this technology into apps that have the potential to be used as screening tools to refer at-risk infants and toddlers for early intervention, when chances for treatment success are greatest. In one study, researchers collected video data of young children watching movies and then used automatic behavioral coding of these videos to quantify children's autism-related behaviors. The researchers found differences in emotion and attention by sex, age, and autism risk status.[2150] Children with ASD also had a higher rate of head movement while watching movies.[2151] Most recently, these researchers developed a mobile app that was successful at distinguishing toddlers diagnosed with ASD from typically developing toddlers based on their eye movements while watching videos.[2152]
- University of California, Davis *(P50HD093079, 2017–2022):* Researchers at this ACE center continue their efforts to classify children into different subgroups of ASD, based on their symptoms, behavioral characteristics, and genetic features, and they aim to develop behavioral and drug interventions appropriate for each subtype. The researchers have found that by age three, about 15 percent of boys with ASD have brains that are disproportionately large relative to the size of their bodies. These boys have a higher rate of regression, or loss of social and communications skills, and are more likely to have an intellectual disability. In contrast, at age three, only three percent of girls with ASD had disproportionately large brains. The researchers plan to follow these children through childhood to determine whether the structure of their brains differ from those of typically developing children.
- Yale University *(P50MH115716, 2017–2022):* Researchers at this Yale ACE center are investigating brain connections in fetuses and newborns to identify early indicators of ASD.[2153] They are also examining whether boys and girls with ASD differ in their brain circuitry, with the aim of improving diagnosis and treatment. In addition, they are evaluating an intervention to improve social functioning in children at high risk for ASD.

[2150] Egger HOL, et al. *NPJ Digit Med.* 2018;1:20. PMID 31304303.
[2151] Dawson G, et al. *Sci Rep.* 2018;8(1):17008. PMID 30451886.
[2152] Chang Z, et al. *JAMA Pediatr*. 2021;175(8):827-836. PMID: 33900383.
[2153] Rolison M, et al. *Cereb Cortex*. 2022 Mar 4;32(6):1212-1222. PMID: 34424949.

- Drexel University *(R01MH115715, 2017–2022):* Investigators in the ACE network based out of Drexel University are evaluating autism screening for toddlers. They are conducting a randomized, controlled trial of 8,000 toddlers to determine whether screening lowers the average age of ASD diagnosis, leads to earlier interventions, and improves outcomes.[2154, 2155]
- Boston Children's Hospital/Harvard Medical School *(U01NS082320, 2012–2019):* This ACE network studied individuals with tuberous sclerosis complex (TSC), a rare genetic disease that causes tumors in the brain and other vital organs.[2156] People with TSC have an increased risk for both autism and epilepsy. Researchers used brain imaging and EEG to track brain development in infants with TSC. They found that early seizure onset negatively impacts neurodevelopment in TSC and that EEG can predict which infants are at risk for developing epilepsy.[2157] Based on these findings, an ongoing NIH-funded clinical trial will assess whether early treatment with vigabatrin, an antiseizure medication, will improve neurocognitive outcomes in infants with TSC.[2158]
- University of California, Davis *(R01MH100030, 2013–2019)*: Researchers at this ACE network have been conducting two controlled trials to identify the effects of intensity and delivery style on developmental progress of toddlers with ASD, and to determine whether toddlers from a previous trial of a specific intervention approach, the Early Start Denver Model, maintain positive effects of treatment after three years.

ACE Centers and Networks with Funding That Ended Before FY 2019

- Mount Sinai School of Medicine *(U01HD073978, 2012–2018):* These ACE network investigators conducted a critical study to understand how genetic and environmental factors influence the development of autism. The team of American and international researchers analyzed detailed records and biospecimens from 4.5 million births involving 20,000 cases of ASD from seven countries (the U.S., Australia, Denmark, Finland, Israel, Norway, and Sweden). The analysis spanned three generations and involve grandparents, parents, aunts, uncles, siblings, and cousins. Results from this study show that inherited genetic factors account for approximately 80 percent of the risk for ASD, leading the researchers to conclude that variation in the occurrence of ASD is likely due to inherited genetic influences, with less contribution from environmental factors.[2159]
- The University of North Carolina at Chapel Hill and Duke University *(U01HD073984, 2012–2017):* This second ACE network at the University of North Carolina evaluated research findings suggesting that treatments with oxytocin nasal spray could 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. In the largest study on the topic to date, researchers found no evidence that a 24-week course of oxytocin improved social interaction or other measures of social function related to ASD.[2160]

[2154] McClure, et al. *Trials 22, 319* (2021). PMID: 33934719.
[2155] Wieckowski AT, et al. *Autism Res*. 2021 Sep;14(9):1923-1934. PMID: 34021728.
[2156] https://www.ninds.nih.gov/Disorders/All-Disorders/Tuberous-Sclerosis-Information-Page
[2157] Wu JY, et al. *Pediatr Neurol*. 2016;54:29-34. PMID: 26498039.
[2158] https://clinicaltrials.gov/ct2/show/NCT02849457
[2159] Bai D, et al. *JAMA Psychiatry*. 2019;76(10):1035-1043. PMID: 31314057.
[2160] Sikich L, et al. *N Engl J Med*. 2021;385(16):1462-1473. PMID: 34644471.

- Wayne State University *(U01NS061264, 2008–2016):* Investigators with the Wayne State ACE network sites conducted a clinical trial to test the safety and efficacy of buspirone, a drug that targets one type of receptor for serotonin (one of several neurotransmitters that brain cells use to communicate with each other) as an early intervention in children with ASD under age six. The trial showed that low-dose buspirone treatment in young children with ASD did not alter overall symptoms of autism. However, analysis of secondary outcome measures showed significant improvement in repetitive and restricted behaviors. The investigators suggest that further research could explore the use of buspirone as an adjunct therapy to target restrictive and repetitive behavior, in combination with other early interventions to address additional ASD symptoms.[2161]
- Boston University *(P50DC013027, 2012–2019):* Researchers at this ACE center studied ASD in children with limited speech and used brain-imaging technologies to understand why certain children with ASD do not learn to speak, with the goal of helping them overcome this limitation. The research team also tested new approaches to help young children with ASD acquire language.
- University of California, Los Angeles *(R01HD073975, 2012–2019):* This UCLA ACE network focused on developing and testing intensive interventions for minimally verbal children with ASD. These interventions were designed to optimize the number of unique socially communicative and unique spoken words. Scientists hope this translational research will identify new intervention mechanisms for nonverbal children with autism.
- Drexel University *(R01ES016443, 2008–2015):* Researchers with this Drexel University ACE network studied possible risk factors and biological indicators of ASD before and soon after birth, as part of the larger Early Autism Risk Longitudinal Investigation effort.
- University of Pittsburgh *(P50HD055748, 2007–2014):* The University of Pittsburgh ACE center studied how people with ASD learn and understand information. Researchers compared information processing, emotional regulation, and brain connectivity in infant siblings; first-diagnosed toddlers with autism; and groups of children, adolescents, and adults with and without autism.
- University of Illinois at Chicago *(P50HD055751, 2007–2014):* Researchers at this ACE center studied genetic factors, brain chemicals, and brain functions that could account for repetitive behaviors in people with ASD. They also tested whether genetic differences influence how individuals respond to certain medications intended to reduce the frequency of these behaviors.
- University of California, San Diego *(P50MH081755, 2007–2014):* Building on earlier studies linking brain development to the risk of autism, investigators at this ACE center showed how patches of disorganization in neuronal cells in the prefrontal cortex of children with ASD were traced back to prenatal development. Both the nature of the cellular disorganization and its specific location in the prefrontal cortex provide more precise targets for researchers to examine potential causes of and treatments for ASD.[2162]
- Yale University *(P50MH081756, 2008–2014):* Researchers conducted studies to search for biomarkers of visual engagement and auditory perception in infants at risk for ASD. Working with

[2161] Chugani DC, et al. *J Pediatr.* 2016;170:45-53. PMID: 26746121.
[2162] Stoner R, et al. *N Engl J Med* 2014;370(13):1209-19. PMID: 24670167.

collaborators from Emory University, scientists from the Yale University ACE center found that focus on eyes was lower among 2- to 6-month-old infants later diagnosed with ASD than in children with typical development. Results from another center study showed that, when viewing significant visual information, such as caregiver faces or peer interaction, typically developing children inhibited eye-blinking earlier than infants who were diagnosed with ASD.[2163]

- University of Washington *(P50HD055782, 2007–2013).* Researchers at the University of Washington ACE center investigated genetic and other factors that might increase a person's risk for ASD and factors that might protect people from developing ASD. Researchers 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.[2164]
- University of California, Davis *(R01MH081757, 2007–2013):* Findings from this ACE network showed that for children with signs of ASD, starting them 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.[2165] 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 at improving parents' sense of personal competence than was participation in a regular community-provided intervention program.[2166] This group also used MRI images to show that high-risk infants who were later diagnosed with ASD had abnormally high volumes of cerebrospinal fluid, which cushions the brain and spinal cord.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the ACE Program

Evaluation Plans

The *Combating Autism Act of 2006* and the *NIH Reform Act of 2006* require that NIH conduct periodic reviews of the ACE program. To implement this requirement, NIH formed the Autism Evaluation Implementation Oversight (AEIO) working group, comprising planning and evaluation officers at the five NIH Institutes (NICHD, NIDCD, NIEHS, NIMH, and NINDS) that provide financial support and scientific expertise to the ACE program.

Between 2013 and 2015, the AEIO working group continued to gather data to assess the implementation and outputs of the ACE program during its intermediate phase, from 2010 through 2014. The findings on research, training, and dissemination activities of the ACE centers and networks, as well as research collaborations and community partnerships, were similar to data in the earlier ACE process evaluation.

The ACE centers and networks have continued to form and participate in partnerships with a variety of public and private organizations, including advocacy groups, pharmaceutical companies, federal agencies, and others. The program is building research capacity in the field by training postdoctoral and early-career

[2163] Shultz S, et al. *Proc Natl Acad Sci USA* 2011;108(52):21270-5. PMID: 22160686.
[2164] Faja S, et al. *J Autism Dev Disord* 2012;42(2):278-93. PMID: 21484517.
[2165] Rogers SJ, et al. *J Am Acad Child Adolesc Psychiatry.* 2012;51(10):1052-65. PMID: 23021480.
[2166] Estes A, et al. *J Autism Dev Disord* 2014;44(2):353-65. PMID: 23838727.

researchers. Data from this program have been shared with the research community through several accessible databases, including NDA, Autism Brain Imaging Data Exchange, Marcus Autism Center Vocal, Autism Speaks Baby Sibs Research Consortium, Autism Genetic Research Exchange, NIMH Repository and Genomics Resource, NLM/NCBI genetic and gene expression data, and NIH Genetics Repository. Scientific findings have been disseminated across numerous venues and forums, including grantee meetings, scientific conferences, workshops and trainings, websites, community forums, press releases, fact sheets and pamphlets, testimony and briefings to legislators, and mass media publications.

Future Directions

NIH convenes an annual, two-day meeting during which investigators present progress toward the goals of their ACE and exchange ideas for collaborations. ACE PIs and project PIs, as well as core directors and data managers, attend. PIs are encouraged to invite K award (career development grant) recipients, fellows, and postdoctoral students from their respective laboratories.

Appendix A: Excerpts of Legal Authorities Related to the NIH Director's Triennial Report to Congress

***PUBLIC HEALTH SERVICE ACT* APPOINTMENT AND AUTHORITY OF DIRECTOR OF NIH SECTION 402**(b) In carrying out the purposes of section 301, the Secretary, acting through the Director of NIH—(7)(A) shall, through the Division of Program Coordination, Planning, and Strategic Initiatives—(ii) include information on such research in reports under section 403.

- -

TRANS-NIH RESEARCH REPORTING

SECTION 402A(c)(2)(B) REPORTING.—Not later than two years after the date of enactment of the *21st Century Cures Act*, the head of each national research institute or national center shall submit to the Director of the National Institutes of Health a report, to be included in the triennial report under section 403, on the amount made available by the institute or center for conducting or supporting research that involves collaboration between the institute or center and one or more other national research institutes or national centers.

- -

TRIENNIAL REPORTS OF DIRECTOR OF NIH

SECTION 403(a) IN GENERAL.—The Director of NIH shall submit to the Congress on a triennial basis a report in accordance with this section. The first report shall be submitted not later than one year after the date of the enactment of the *National Institutes of Health Reform Act of 2006*. Each such report shall include the following information:

(1) An assessment of the state of biomedical and behavioral research.
(2) A description of the activities conducted or supported by the agencies of the National Institutes of Health and policies respecting the programs of such agencies.
(3) A description of intra-National Institutes of Health activities, including—
    (A) identification of the percentage of funds made available by each national research institute and national center with respect to each applicable fiscal year for conducting or supporting

research that involves collaboration between the institute or center and one or more other national research institutes or national centers; and

(B) recommendations for promoting coordination of information among the centers of excellence.

(4) A catalog of all the research activities of the agencies, prepared in accordance with the following:

(A) The catalog shall, for each such activity—

(i) identify the agency or agencies involved;

(ii) state whether the activity was carried out directly by the agencies or was supported by the agencies and describe to what extent the agency was involved;

and

(iii) identify whether the activity was carried out through a center of excellence.

(B) In the case of clinical research, the catalog shall, as appropriate, identify study populations by demographic variables, including biological and social variables and relevant age categories (such as pediatric subgroups), and determinants of health, that contribute to research on minority health and health disparities.

(C) Research activities listed in the catalog shall include, where applicable, the following:

(i) Epidemiological studies and longitudinal studies.

(ii) Disease registries, information clearinghouses, and other data systems.

(iii) Public education and information campaigns.

(iv) Training activities, including—

(I) National Research Service Awards and Clinical Transformation Science Awards;

(II) graduate medical education programs, including information on the number and type of graduate degrees awarded during the period in which the programs received funding under this title;

(III) investigator-initiated awards for postdoctoral training and postdoctoral training funded through research grants;

(IV) a breakdown by demographic variables and other appropriate categories; and

(V) an evaluation and comparison of outcomes and effectiveness of various training programs.

(v) Clinical trials, including a breakdown of participation by study populations and demographic variables, including relevant age categories (such as pediatric subgroups), information submitted by each national research institute and national center to the Director of National Institutes of Health under section 492B(f), and such other information as may be necessary to demonstrate compliance with section 492B and other applicable requirements regarding inclusion of demographic groups.

(vi) Translational research activities with other agencies of the Public Health Service.

(5) A summary of the research activities throughout the agencies, which summary shall be organized by the following categories, where applicable:

(A) Cancer.

(B) Neurosciences.

(C) Life stages, human development, and rehabilitation.

(D) Organ systems.

(E) Autoimmune diseases.

(F) Genomics.

(G) Molecular biology and basic science.

(H) Technology development.

(I) Chronic diseases, including pain and palliative care.
(J) Infectious diseases and bioterrorism.
(K) Minority health and health disparities.
(L) Such additional categories as the Director determines to be appropriate.

(6) A review of each entity receiving funding under this title in its capacity as a center of excellence (in this paragraph referred to as a "center of excellence"), including the following—

(A) An evaluation of the performance and research outcomes of each center of excellence.
(B) Recommendations for improving the effectiveness, efficiency, and outcomes of the centers of excellence.

(b) REQUIREMENT REGARDING DISEASE-SPECIFIC RESEARCH ACTIVITIES.—In a report under subsection (a), the Director of NIH, when reporting on research activities relating to a specific disease, disorder, or other adverse health condition, shall—

(1) present information in a standardized format;
(2) identify the actual dollar amounts obligated for such activities; and
(3) include a plan for research on the specific disease, disorder, or other adverse health condition, including a statement of objectives regarding the research, the means for achieving the objectives, a date by which the objectives are expected to be achieved, and justifications for revisions to the plan.

(c) ADDITIONAL REPORTS.—In addition to reports required by subsections (a) and (b), the Director of NIH or the head of a national research institute or national center may submit to the Congress such additional reports as the Director or the head of such institute or center determines to be appropriate.

- -

SCIENTIFIC FRAMEWORK FOR RECALCITRANT CANCERS

SECTION 417G

(d) REPORTING.—

(1) BIENNIAL REPORTS.—The Director of NIH shall ensure each biennial[2167] 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.

[2167] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

(C) An update on activities pertaining to such cancer under the authority of section 413(b)(7).

- -

OFFICE OF RESEARCH ON WOMEN'S HEALTH

SECTION 486(d)(5) ADVISORY COMMITTEE.—

(A) The Advisory Committee shall prepare a biennial report describing the activities of the Committee, including findings made by the Committee regarding—
  (i) compliance with section 492B;
  (ii) the extent of expenditures made for research on women's health by the agencies of the National Institutes of Health; and
  (iii) the level of funding needed for such research.

(B) The report required in subparagraph (A) shall be submitted to the Director of NIH for inclusion in the report required in section 403.

- -

BIENNIAL REPORT

SECTION 486B(a) IN GENERAL.—With respect to research on women's health, the Director of the Office shall, not later than February 1, 1994, and biennially thereafter, prepare a report—

(1) describing and evaluating the progress made during the preceding two fiscal years in research and treatment conducted or supported by the National Institutes of Health;
(2) describing and analyzing the professional status of women physicians and scientists of such Institutes, including the identification of problems and barriers regarding advancements;
(3) summarizing and analyzing expenditures made by the agencies of such Institutes (and by such Office) during the preceding two 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[2168] 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.

[2168] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

- -

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

SECTION 492B(f) REPORTS BY ADVISORY COUNCILS.—The advisory council of each national research institute shall prepare triennial reports describing the manner in which the institute has complied with this section. Each such report shall be submitted to the Director of the institute involved for inclusion in the triennial report under section 403.

- -

HUNTER KELLY RESEARCH PROGRAM

SECTION 1116(c) REPORTS.—The Director is encouraged to include information about the activities carried out under this section in the biennial[2169] 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.

- -

MICROBICIDE RESEARCH

SECTION 2351A(a) FEDERAL STRATEGIC PLAN.—The Director of the Office shall—

(1) expedite the implementation of the Federal strategic plans required by section 403(a) of the *Public Health Service Act* (42 U.S.C. 283(a)(5)) regarding the conduct and support of research on, and development of, a microbicide to prevent the transmission of the human immunodeficiency virus; and
(2) review and, as appropriate, revise such plan to prioritize funding and activities relative to their scientific urgency and potential market readiness.

- -

[2169] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

***NATIONAL INSTITUTES OF HEALTH REFORM ACT OF 2006*, P.L. 109-482**

ENHANCING THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD

SECTION 106 (codified as a note in 42 USC 284)

(a) IN GENERAL.—In administering the Clinical and Translational Science Award, the Director of NIH shall establish a mechanism to preserve independent funding and infrastructure for pediatric clinical research centers by—

(1) allowing the appointment of a secondary principal investigator under a single Clinical and Translational Science Award, such that a pediatric principal investigator may be appointed with direct authority over a separate budget and infrastructure for pediatric clinical research; or
(2) otherwise securing institutional independence of pediatric clinical research centers with respect to finances, infrastructure, resources, and research agenda.

(b) REPORT.—As part of the biennial[2170] 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).

- -

***21ST CENTURY CURES ACT*, P.L. 114-255**

EUREKA PRIZE COMPETITIONS

SECTION 2002 (codified in 42 USC 283q)

(b) TRACKING; REPORTING.—The Director of the National Institutes of Health shall—

(1) collect information on—
    (A) the effect of innovations funded through the prize competitions under this section in advancing biomedical science or improving health outcomes pursuant to subsection (a); and
    (B) the effect of the innovations on Federal expenditures; and

[2170] *21st Century Cures Act* (P.L. 114-255) amended Section 403 to require the report to Congress to be submitted on a triennial basis.

(2) include the information collected under paragraph (1) in the triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032).

- -

APPROPRIATE AGE GROUPINGS IN CLINICAL RESEARCH

SECTION 2038(i)(3) PUBLIC AVAILABILITY OF FINDINGS AND CONCLUSIONS.—The Director of the National Institutes of Health shall –

(A) make the findings and conclusions resulting from the workshop under paragraph (1) and updates to policies in accordance with paragraph (2), as applicable, available to the public on the Internet website of the National Institutes of Health; and

(B) ensure that age-related data reported in the triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032) are made available to the public on the Internet website of the National Institutes of Health.

- -

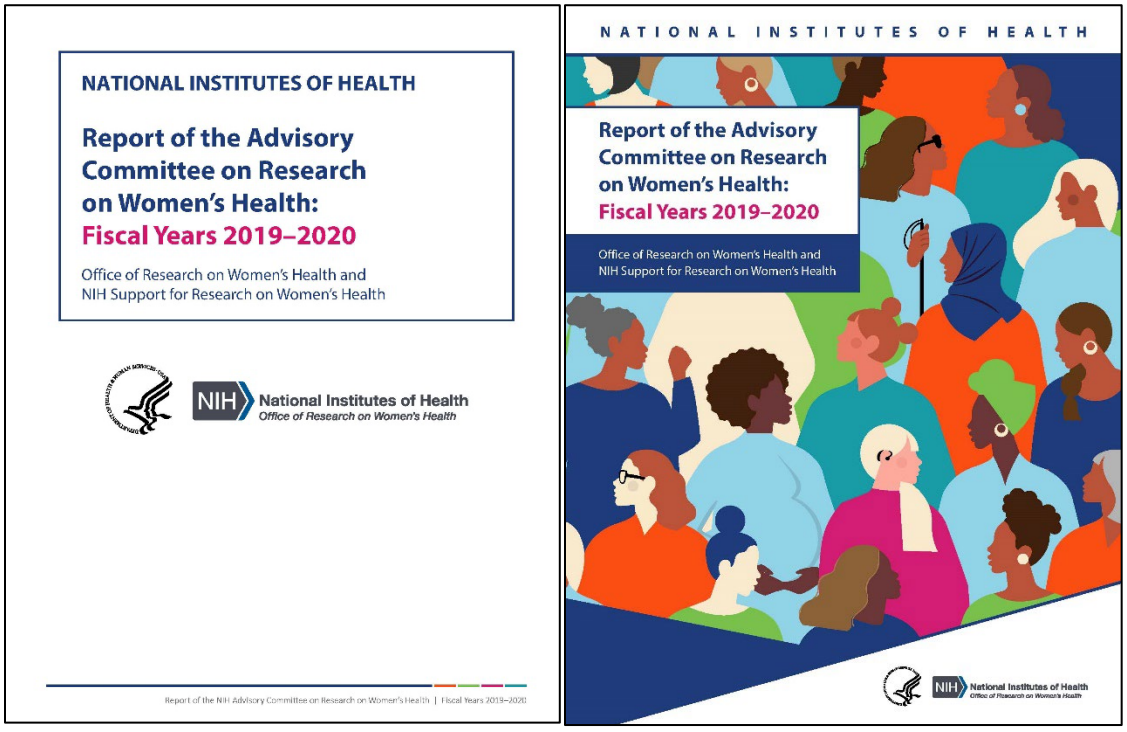
TICK-BORNE DISEASES

SECTION 2062(a) IN GENERAL.—The Secretary of Health and Human Services (referred to in this section as ‘‘the Secretary’’) shall continue to conduct or support epidemiological, basic, translational, and clinical research related to vector-borne diseases, including tick-borne diseases.

(b) REPORTS.—The Secretary shall ensure that each triennial report under section 403 of the *Public Health Service Act* (42 U.S.C. 283) (as amended by section 2032) includes information on actions undertaken by the National Institutes of Health to carry out subsection (a) with respect to tick-borne diseases.

Appendix B: Report of the Advisory Committee on Research on Women's Health

This report details the NIH-wide programs and accomplishments carried out in fulfillment of the core mission of the NIH Office of Research on Women's Health. The report also provides highlights from research on women's health and on the influence of sex and gender on health and disease supported by NIH Institutes, Centers, and the NIH Office of the Director. New to the report for FY 2019 and FY 2020 is the section titled "NIH Workforce and Grantees." This section includes two subsections. The first one provides information on roles, programs, and occupations of women in the NIH workforce for FY 2019–2020; and the second one provides information on NIH grant funding by sex and/or gender, race, and ethnicity for FY 2016–2020. In addition, the report presents NIH women's health research spending for FY 2019, including data from FY 2017–2018 for comparison purposes. Finally, the report documents the inclusion of women and racial and ethnic minorities in NIH-funded clinical research during these years. For the full report, please see:
https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_BiennialReport2019_20_508.pdf



Appendix C: Actions Undertaken to Conduct or Support Research Related to Vector-Borne Diseases

NIH conducts and supports a comprehensive research program to advance science and identify approaches to prevent, diagnose, and treat vector-borne diseases and to control the vectors that transmit these diseases to humans. During FY 2019 – FY 2021, NIH committed between $611 million and $731 million each year to vector-borne disease research.[2171] To satisfy legislative requirements included in the *21st Century Cures Act* (P.L. 114-255), NIH has developed the following report of epidemiological, fundamental, translational, and clinical research related to vector-borne diseases, including tickborne diseases (TBDs).[2172] This report is not comprehensive, but rather provides a representative cross-section of vector-borne disease research supported by NIH. A comprehensive listing of vector-borne disease activities supported by NIH can be found on the NIH Research Portfolio Online Reporting Tools (RePORT) website.[2173]

Background

Vectors, including insects and ticks, can transmit many infectious disease pathogens to people. Diseases spread by vectors such as mosquitoes or ticks are a serious public health threat that account for more than 17 percent of all infectious diseases, according to the World Health Organization (WHO).[2174] In the last decade, outbreaks of mosquito-transmitted viruses such as dengue, Zika, and chikungunya in the Americas attest to the importance of maintaining a foundation of research and development efforts to respond effectively to these emerging infectious diseases.

In the U. S., Lyme disease is the most common reported TBD, accounting for more than 80 percent of all reported TBD cases.[2175] Among nationally notifiable infectious diseases, Lyme disease is the fifth most commonly reported, with 30,000 cases annually.[2176] However, the scope of the problem may be greater than the number of cases initially reported. Studies by the CDC estimate that the number of U.S. patients treated for Lyme Disease may exceed reported cases 10-fold, approximating 465,000 patients annually.[2177]

Current strategies to address TBDs are hindered by suboptimal diagnostics, a paucity of treatment options, a lack of vaccines, and ineffective tick control approaches. In 2019, the NIH published the NIH

[2171] https://report.nih.gov/categorical_spending.aspx
[2172] See Appendix A for language in the *Public Health Service Act*, as amended by the *21st Century Cures Act* (P.L. 114-255), that is relevant to these requirements.
[2173] https://report.nih.gov/categorical_spending.aspx
[2174] https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases
[2175] https://www.cdc.gov/lyme/datasurveillance/index.html
[2176] https://www.cdc.gov/lyme/datasurveillance/index.html
[2177] https://www.cdc.gov/lyme/datasurveillance/index.html

Strategic Plan for Tickborne Disease Research, proposing additional research to better understand the complex interplay among host, tick, and pathogen factors that contribute to TBDs and the body's defenses against them.

NIH continues to support basic, translational, and clinical research into new vector control interventions and transmission-prevention strategies. These studies include research on the relationship of arthropod vectors with their environment, the pathogens they transmit, and the vertebrate hosts they feed on. By understanding the mechanisms involved in these interactions, researchers can identify potential targets to prevent vectors from blood feeding or from transmitting pathogens to humans.

NIH also supports research to understand the impact of vector-borne pathogens infection on the human host and how they cause disease. Basic research efforts seek to identify critical cellular and molecular pathways involved in disease pathogenesis, the human immune system response, and how signaling pathways that impact multiple organ systems can lead to common symptoms, such as arthritis or skin conditions. In addition, examining of the role of proteins in the insect's saliva and the interactions between the vector, pathogen, and the immune system and microbiome is informing the development of broadly protective vaccine candidate for vector-borne diseases.

The increase in vector-borne disease incidence in the U.S. represents a growing public health threat as new pathogens emerge and the geographic distributions of vectors change. Unlike infectious diseases that spread directly from person to person or through intermediate surface contact, vector-borne diseases are transmitted through a complex interplay of human hosts, pathogens, vectors, and animal reservoirs. Wild and domestic animals, including mammals, reptiles, and birds, are often important players in vector-borne pathogen survival, reproduction, and spread. NIH is committed to conducting and supporting research to better understand the biology of vectors, how they transmit diseases, and how they find and interact with human or animal hosts, with the goal of developing and improving strategies to prevent the transmission of these diseases to humans.

NIH Actions to Support Vector-Borne Disease Research

Research Updates

Chikungunya

Chikungunya virus (CHIKV) is transmitted to people via the bite of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes.[2178] Viral reservoirs include humans, rodents, birds, monkeys, and other animals. CHIKV was discovered in Tanzania in 1952 and has caused numerous outbreaks of chikungunya, a severe, debilitating, febrile, arthritic disease prevalent in Africa and the Indian Ocean region. Early symptoms of chikungunya disease are similar to those of dengue, making differential diagnosis difficult early in the infection. Since 2013, CHIKV has spread rapidly into parts of Europe, the Caribbean Islands, and Central and South America. Severe neonatal infection can occur at birth if the mother is infected with CHIKV. No licensed vaccines or therapeutics exist for this disease.

[2178] https://www.cdc.gov/chikungunya/transmission/index.html

Fundamental Research

- Demonstrated that the interferon-stimulated gene *E74-like ETS transcription factor 1* (ELF1), when expressed exogenously, inhibits chikungunya virus and yellow fever virus infection (R01AI143639) *(NIAID)*

Translational Research

- Identified antibodies from Chikungunya virus-seropositive individuals with the potential to serve as pan-alphavirus therapeutics *(NIAID)*

Clinical Research

- Demonstrated that the chikungunya virus–like particle vaccine (CHIKV VLP) was safe, well-tolerated, and immunogenic in phase 2 trial in healthy adults in a CHIKV endemic population (NCT02562482) *(NIAID)*

Dengue Fever

Dengue fever, a common mosquito-borne viral disease, occurs in most tropical and subtropical regions of the world.[2179] Dengue fever is caused by four serotypes of dengue virus (DENV), a flavivirus transmitted to humans by *A. aegypti* and *A. albopictus* mosquitoes, which thrive in urban and semiurban environments. Most people infected with DENV experience no symptoms or only a mild fever. Others develop flu-like symptoms, headache, and joint and muscle pain. A subset experience more severe symptoms, which can cause high fever, pain, bleeding, a sudden drop in blood pressure and, in some cases, shock syndrome and death.

Epidemiological Research

- Determined that Zika virus infection enhances future risk of severe dengue disease *(NIAID)*

Fundamental Research

- Determined susceptibility to severe dengue disease through antibody configuration during secondary infection *(NIAID)*
- Maternal anti-dengue IgG fucosylation predicts susceptibility to dengue disease in infants *(NIAID)*
- Determined that flavivirus NS1 triggers tissue-specific vascular endothelial dysfunction reflecting disease tropism *(NIAID)*
- Improved the *Aedes aegypti* reference genome to enhance research on control approaches *(NIAID)*
- Discovered the human odors that attract mosquitoes *(NIAID)*

Translational Research

- Determined the structural basis for antibody inhibition of flavivirus NS1-triggered endothelial dysfunction *(NIAID)*

Clinical Research

- Conducted controlled human infection studies to test antiviral JNJ-D1863 *(NIAID)*

[2179] https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

- Supported phase 1 clinical trial for a broad-spectrum monoclonal (mAb) against dengue *(NIAID)*
- Developed and evaluated a tetravalent dengue vaccine containing each serotype that can be used in endemic areas in all age groups in phase 2 and 3 trials (*NIAID)*
- Supported two clinical trials to assess the impact of mosquito-based interventions on dengue infections *(NIAID)*

Lyme Disease and Other Tickborne Diseases

Ticks are capable of transmitting a variety of disease-causing pathogens, including those responsible for Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, babesiosis, and Powassan disease.[2180] Lyme disease, the most prevalent of the tick-transmitted infections in the U.S., is caused by the bacterium *Borrelia burgdorferi*. It causes such symptoms as fever, headache, stiff neck, body aches, fatigue, and, in some individuals, a rash at the site of the tick bite that looks like a bull's eye. For reasons that are still unclear, a small percentage of patients report a range of sometimes debilitating symptoms, known as Post-treatment Lyme disease syndrome (PTLDS), continuing years after standard antibiotic treatment. NIH supports an extensive and diverse research portfolio to advance understanding of Lyme disease and other TBDs and to better diagnose, prevent, and treat these conditions.

Fundamental Research

- Examined the interactions between black-legged ticks and mammals and learned that flaviviruses reproduce in specific locations in the tick salivary gland cultures *(NIAID)*
- Examined host blood-meal mechanisms that dictate pathogenic potential of the Lyme disease within the tick vector *(NIAID)*
- Identified *Borrelia burgdorferi* peptidoglycan as a persistent antigen in patients with Lyme arthritis *(NIAID)*
- Developed a new tool for molecular genetic investigations in *B. burgdorferi,* allowing visualization of living cells *(NIAID)*
- Developed an approach to manipulate tick genes/genome to better understand their function *(NIAID)*
- Discovered that black-legged ticks are able to survive toxic human skin bacteria using a toxin that kills such bacteria *(NIAID)*

Translational Research

- Developed a post-treatment Lyme disease symptom score to help quantitate the diversity of Lyme disease patients with and without residual non-specific symptoms after therapy *(NIAID)*
- Developed an optical design for high accuracy automated tick classification called VecTech *(NIAID)*
- Developed experimental vaccine against Crimean-Congo hemorrhagic fever virus, a lethal tickborne virus, that was protective in nonhuman primates (NHPs) *(NIAID)*

Clinical Research

- Developed Point-of-Care Diagnostic Test for Lyme Disease *(NIAID)*

[2180] https://www.cdc.gov/ticks/diseases/index.html

- Enrolled more than 500 patients in clinical studies at the NIH Clinical Center representing a broad spectrum of Lyme-associated illnesses, including patients with classical Lyme disease, PTLDS, and those who have recovered from Lyme disease. Ongoing studies include:
    - Evaluation, treatment, and follow-up of Lyme disease patients to assess clinical course and outcomes and to define immune response to infection (NCT0028080) *(NIAID)*
    - Evaluation of patients with PTLDS (NCT00001539) *(NIAID)*
    - Evaluation of xenodiagnosis to test for the presence of *B. burgdorferi* infection in patients following antibiotic treatment (NCT02446626) *(NIAID)*

Malaria

Human malaria, caused by parasites (*Plasmodium falciparum* and others) and transmitted by *Anopheles* mosquitoes, remains the most significant parasitic disease globally in terms of annual mortality. Considerable progress has been made in the global fight to control and eliminate malaria through improved prevention and control efforts. In 2020, there were an estimated 241 million malaria cases and 627,000 malaria deaths, according to the WHO.[2181] Despite the progress made to curb malaria's global impact, nearly half of the world's population remains at risk. NIH is leveraging its comprehensive research program to achieve the goal of eliminating malaria.

Epidemiological Research

- Determined long-distance migration of malaria mosquitoes and consequent impacts on transmission and control *(NIAID)*
- Demonstrated malaria infection in Mali is common and associated with perinatal mortality and preterm delivery despite widespread use of chemoprevention *(NIAID)*
- Determined sources of persistent malaria transmission in a setting with effective malaria control in eastern Uganda *(NIAID)*

Fundamental Research

- Determined that exposing *Anopheles* mosquitoes to antimalarials blocks *Plasmodium* parasite transmission *(NIAID)*
- Determined that manipulated Metarhizium fungi can kill Anopheles mosquitoes *(NIAID)*
- Determined the effect of ambient temperature in the ability of Anopheles mosquitoes to feed and transmit malaria to humans *(NIAID)*
- Identified a symbiotic bacteria that blocks malaria parasite development in the mosquito *(NIAID)*
- Discovered an important role for cytotoxic lymphocytes, a type of T cell, in cerebral malaria *(NINDS)*

Translational Research

- Discovered a potent anti-malarial human monoclonal antibody that targets circumsporozoite proteins and neutralizes sporozoites *(NIAID)*
- Used quantitative plasma proteomics to identify biomarkers of malarial anemia that may point to underlying mechanisms (NCT01168271) *(NIAID)*

[2181] https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

- Developed a preclinical activated T-cell metabolism inhibitor (6-diazo-5-oxo-L-norleucine (DON)) as treatment for cerebral malaria which is planned for phase 1 clinical trial in 2022 *(NIAID)*
- Utilized the NCATS Malaria Active Collection for small molecule screening across the Plasmodium lifecycle to yield insight into the pathogen and identify novel active compounds *(NCATS)*
- Developed a high-throughput assay to assess transmission blocking activity against the malaria parasite and demonstrated that some clinically used antimalarials are able to inhibit parasite fertilization and early development within the mosquito vector, supporting further evaluation for community-wide control efforts *(NCATS/NIAID)*
- Developed a high-throughput assay for the evaluation of triple artemisinin-based combination therapies (TACTs) against Plasmodium parasites and demonstrated specific parasite genotypes with decreased susceptibility to TACT combinations *(NCATS/NIAID)*

Clinical Research

- Conducted phase 1 trial to assess safety and pharmacokinetics of monoclonal antibody (CIS43LS) to prevent malaria, and demonstrated protection in a controlled human malaria infection (CHMI) (NCT04206332) *(NIAID)*
- Optimized regimens for chemoprophylaxis vaccination demonstrating strong and lasting protection against malaria *(NIAID)*
- Demonstrated that a seasonal malaria chemoprevention regimen reduced infections and malaria-induced immune dysfunction in children *(NIAID)*
- Supported a clinical trial to assess the impact of ivermectin on mosquito survival and malaria transmission *(NIAID)*

West Nile

West Nile virus (WNV) is a flavivirus that primarily cycles between mosquitoes and birds but can be transmitted to humans through the bite of an infected *Culex* mosquito.[2182] WNV is well established in the U.S. and many countries in Europe and the Middle East. Most serious cases occur in people older than 50 years of age and in those with impaired immune systems. In a small number of cases, WNV has been spread via blood transfusions, organ transplants, and breastfeeding.

Fundamental Research

- Demonstrated that T regulatory cells participate in disease tolerance in the context of WNV infection by tuning an appropriately focused and balanced immune response to control the virus while minimizing immunopathology and clinical disease (*NIAID)*
- Demonstrated WNV infection of the CNS disrupts the immune-neural-synaptic axis via induction of pleiotropic gene regulation of host responses *(NIAID)*

Translational Research

- Identified a potently neutralizing human monoclonal antibody targeting an epitope in the WNV E protein preferentially recognizes mature virions *(NIAID)*

[2182] https://www.cdc.gov/westnile/transmission/index.html

Zika

Zika virus (ZIKV) is primarily transmitted to humans through the bite of infected *A. aegypti* mosquitoes.[2183] ZIKV can be transmitted from an infected woman to her baby during pregnancy and can result in serious birth defects, including microcephaly. In May 2015, the Pan American Health Organization issued an alert regarding the first confirmed ZIKV infection in Brazil. Since that time, Brazil and other countries and territories in Central and South America, as well as the Caribbean (including Puerto Rico and the U.S. Virgin Islands) have experienced ongoing ZIKV transmission. NIH is working with its partners in government, academia, and the pharmaceutical and biotechnology industries to better understand ZIKV, the disease it causes, and ways to combat it.

Epidemiological Research

- Monitored blood donors from 2016 to present at four large blood centers in Brazil for the presence of ZIKV as well as CHIKV and Dengue viruses for assessment of incidence of these viruses in four large geographically dispersed regions in Brazil *(NHLBI)*

Fundamental Research

- Identified mechanism of viral tropism and ZIKV pathogenesis in the male and female reproductive organs *(NIAID)*
- Identified a critical regulator of mitophagy, which removes damaged mitochondria, and demonstrated a role for mitophagy in limiting systemic inflammation following infection by ZIKV *(NIAID)*
- Determined that ZIKV envelope protein modification drives ZIKV entry and pathogenesis *(NIAID)*
- Launched study on molecular regulatory mechanism of Zika virus-induced intracranial calcifications *(NIDCR)*
- Launched study to define the craniofacial and dental phenotypes of children exposed to the ZIKV during gestation, with biological samples collected for future studies related to the impact of the virus *(NIDCR)*

Translational Research

- Determined that white blood cells in the placenta of pregnant mice infected with ZIKV prevented the virus from entering the developing pup, protecting it from infection *(NIAID)*
- Developed a vaccine that lowered levels of virus in pregnant NHPs and improved fetal outcomes in a congenital model of ZIKV infection *(NIAID)*
- Utilized a variety of advanced drug screening techniques to test out more than 10,000 compounds in search of a cure for ZIKV infections, finding that the widely used antibiotic methacycline was effective at preventing brain infections and reducing neurological problems associated with the virus in mice *(NCATS/NINDS)*
- Evaluated in a macaque model the minimal infectious dose that leads to transfusion-transmission of ZIKV by blood products, and determined that transfusion of plasma containing antibodies to

[2183] https://www.cdc.gov/zika/about/index.html

ZIKV appeared to significantly decrease the risk of the virus being transmissible by transfusion *(NHLBI)*

- Developed live attenuated Zika vaccine candidates that are co-formulated with a tetravalent dengue vaccine *(NIAID)*

Clinical Research

- Determined that history of dengue virus infection significantly lowered the risk of being symptomatic when infected by ZIKV *(NIAID)*
- Established ZIKV infection enhanced future risk of severe dengue disease *(NIAID)*
- Completed a phase 2/2B clinical trial evaluating safety, immunogenicity and efficacy of a ZIKV DNA vaccine in Zika endemic/potential endemic regions (NCT031100770) *(NIAID)*
- Established a sharable biorepository, containing biospecimens from ZIKV-infected blood donors who participated in the 2016-2018 U.S. Donor Natural History Study to enable global standardized evaluation of molecular and immunologic blood screening and diagnostic tests for ZIKV infection and accelerate knowledge on test performance *(NHLBI)*
- Analyzed viral and antibody persistence in biospecimens from the 2016-2018 U.S. Donor Natural History and determined that red Blood Cell-associated ZIKV RNA persists well beyond that in plasma indicating that blood screening of plasma is sufficient *(NHLBI)*

Other Vector-Borne Diseases

Fundamental Research

- Supported research into how mosquitoes smell their prey, feed as larvae, find each other to mate, and how these important processes could be blocked with new pesticides or repellants to help limit transmission of mosquito-borne diseases such as Eastern equine encephalitis virus (EEEV) *(NIAID)*
- Discovered that many mosquito species use wind to migrate after taking a blood meal and thus may be spreading pathogens over hundreds of kilometers and revealed diversity, dynamics, direction, and magnitude of these high-altitude migrating insects in the Sahel region of Africa *(NIAID)*
- Developed a novel, simple, no/low-impact and long-lasting marking method that allows separation of multiple insect subpopulations *(NIAID)*
- Revealed structure and mechanism of action of salivary complement inhibitors from mosquitoes *(NIAID)*
- Demonstrated sand fly salivary protein acts as a neutrophil chemoattractant *(NIAID)*
- Showed fatal visceral leishmaniasis is associated with intestinal parasitism and secondary infection by commensal bacteria in model organisms and is delayed by antibiotic prophylaxis *(NIAID)*

Translational Research

- Developed a vector-based (sand fly saliva protein) pan-Leishmania vaccine through reverse vaccinology and provided proof of principle of potential effectiveness in humans *(NIAID)*

Clinical Research

- Discovered protozoan parasites spread by mosquitoes that mimic the symptoms of visceral leishmaniasis in people *(NIAID)*
- Demonstrated safety and immunogenicity in a phase 1 clinical trial of a virus-like particle vaccine candidate against EEEV and the related western equine encephalitis virus and Venezuelan equine encephalitis virus *(NIAID)*
- Demonstrated that a novel vaccine candidate targeting mosquito saliva to prevent a variety of mosquito-borne infections, including EEEV, is safe and immunogenic in humans. An improved version of the vaccine is now undergoing a phase 1 trial (NCT04009824) *(NIAID)*
- Completed critical toxicology studies necessary to enable the partners at the Drugs for Neglected Diseases initiative to complete pivotal phase 2/3 trials for the use of Acoziborole, a cost-effective, easy-to-administer oral therapy that requires only one dose, to treat Human African Trypanosomiasis (HAT, or Sleeping Sickness) *(NCATS)*

Vector Control Strategies

NIH conducts and supports a comprehensive vector biology research program to advance science and identify approaches that will help control or prevent the transmission of vector-borne pathogens to humans. This program includes a variety of basic, translational, and clinical research projects that will contribute to a better understanding of key aspects of the biology of arthropod vectors that can be potential targets for control approaches. The translational program supports the development of products to reduce vector populations, prevent vectors from coming into contact with people, or killing the pathogen within the vector. The clinical projects evaluate products and approaches designed to prevent the transmission of vector-borne pathogens to humans.

Translational Research

- Integrated *Wolbachia*-based and auto-dissemination approaches to control *Aedes* mosquitoes for an innovative solution called MosquitoMate *(NIAID)*
- Developed SpringStar AGO Traps, autocidal traps that attract female mosquitos searching for sites to lay eggs, killing the female and the larvae *(NIAID)*

Committees

- Trans-NIH Tick Borne Diseases Strategic Planning Team was convened with subject matter policy experts from five NIH institutes and the NIH Office of the Director to develop a strategic framework to advance TBD research for the next five years and beyond. The framework outlined five areas of opportunity in TBD research, including improving fundamental knowledge, diagnosis, prevention, treatment, and research tools and resources. (NIAID)
- The Federal Vector-borne Disease Integrated Pest Management Working Group permits agency representatives to discuss updates and important developments regarding vector-borne diseases, particularly vector control. *(NIAID)*
- The HHS Tickborne Disease Working Group was established by Congress in 2016 as part of the *21st Century Cures Act* to provide subject-matter expertise and to review federal efforts related to all TBDs, to help ensure interagency coordination and minimize overlap, and to examine

research priorities. Representatives from NIAID participate in this committee. The first working group report to Congress was submitted to Congress in November 2018. *(NIAID)*

- The Tularemia Animal Model Qualification Working Group collaborates on the qualifications of primate models of pneumonic tularemia under the FDA Animal Model Qualification/Drug Development Tools Program. The collaboration includes the exchange of study data, study reports, and agreements on a regulatory strategy for model qualification. *(NIAID)*
- The U.S. Government Zika Vaccine Development Interagency Working Group was established by HHS and includes representatives from various U.S. government agencies (BARDA, CDC, DoD, FDA, NIH, WRAIR) to coordinate research efforts, mobilize domestic and international research infrastructure, and form partnerships with industry to accelerate the development of a safe and effective ZIKV vaccine. *(NIAID)*

Programs

- The International Centers of Excellence for Malaria Research (ICEMR) is a global network established to better understand malaria in endemic settings and strengthen local research capacity. The ICEMR program partners with the Bill & Melinda Gates Foundation to address important malaria-related research questions. *(NIAID)*
- NIAID DIR International Centers for Excellence in Research (ICER) was launched in 2002 to develop and sustain research programs in resource-poor countries through partnerships with local scientists. DIR's sites in Mali, Uganda, and India have fostered expanded local research capacity through training young scientists, improving laboratory and clinical infrastructure, and enhancing IT capabilities. A major focus is research into vector-borne diseases. The Mali ICER program builds on experience gained from NIAID's long-standing malaria research collaboration with scientists in Mali and hosts multiple projects, including studies on mosquito vectors, malaria drug resistance, and candidate malaria vaccines. Research on other vector-borne neglected tropical diseases such as leishmaniasis and Crimean-Congo hemorrhagic fever virus is also performed. *(NIAID)*
- The NIAID Vector Biology Program conducts and supports a comprehensive vector biology research program to advance science and identify and test approaches that will help control or prevent the transmission of vector-borne pathogens to humans. This research includes the development of traps and repellents, the testing of such biologicals as *Wolbachia* bacteria, and the evaluation of novel candidate vaccines based on mosquito saliva. *(NIAID)*
- The Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) is a blood safety research program designed to ensure safe and effective blood banking and transfusion medicine practices. The program is poised to conduct targeted research studies in the U.S. and Brazil that can evaluate an emerging infectious agent (such as an arbovirus) quickly for its prevalence and incidence among blood donors, transfusion-transmission potential, risk factors, and/or clinical relevance to the blood recipient population. The program is currently conducting research to detect and report changes in the incidence of ZIKV, DENV, and CHIKV in blood donors in Brazil. Prior studies have characterized the evolving viral and serological stages of ZIKV infection, evaluated ZIKV RNA and IgM persistence in blood compartments and body fluids, and estimated the incidence of infection during the 2016 Puerto Rican Zika epidemic. Results from this body of research inform worldwide

blood screening policies and strategies for preventing transmission of these viruses via blood transfusion. *(NHLBI)*

- Therapeutics for Rare and Neglected Diseases (TRND) program encourages and speeds the development of new treatments for diseases with high unmet medical needs. This includes vector-borne tropical diseases, such as schistosomiasis and malaria. TRND stimulates therapeutic development research collaborations among NIH and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies working on rare and neglected illnesses. *(NCATS)*
- The Tropical Medicine Research Centers support a variety of efforts focused on neglected vector-borne diseases. These centers facilitate research on the cause, diagnosis, prevention, and treatment of neglected tropical diseases and work toward the creation of sustainable in-country research capacity. *(NIAID)*
- Zika in Infants and Pregnancy (ZIP) is a multi-country study to evaluate the magnitude of health risks that ZIKV poses to pregnant women and their developing fetuses and infants. *(NIAID, NICHD, NIEHS)*
- Immune Response to Arthropod Blood Feeding program was designed to understand the immunologic events that occur during blood feeding by hematophagous arthropods, which facilitate vector-borne pathogen transmission. NIH has received grant applications focused on vector-borne pathogens including DENV, ZIKV, arbovirus, Borrelia burgdorferi, Powassan virus, Plasmodium vivax, CCHFV, Leishmania, *Orientia tsutsugamushi*, *Trypanosoma brucei, Ehrlichia chaffeensis*. *(NIAID)*
- Collaborative Cross Mouse Model Generation and Discovery of Immunoregulatory Mechanisms program was designed to support the use of Collaborative Cross (CC) mouse lines to advance understanding of the host genetics involved in immune regulation and function and to further develop CC mouse lines that more faithfully reproduce human immune responses. NIH has received grant applications focused on vector-borne pathogens including *Borrelia burgdorferi*, *Plasmodium yoelii, Borrelia recurrentis,* WNV, JEV, POWV, and Rift Valley fever virus. *(NIAID)*
- The Centers for Research in Emerging Infectious Diseases (CREID) Network is a coordinated group of emerging infectious disease research centers situated in regions around the globe where emerging and re-emerging infectious disease outbreaks are likely to occur. Multidisciplinary teams of investigators will conduct pathogen/host surveillance, study pathogen transmission, pathogenesis and immunologic responses in the host, and will develop reagents and diagnostic assays for improved detection for important emerging pathogens and their vectors. They plan to prospectively develop a framework and the infrastructure necessary to respond quickly and effectively to future outbreaks. *(NIAID)*
- The Models of Infectious Disease Agent Study (MIDAS) is a collaboration of research and informatics groups that develop computational models of the interactions between infectious agents and their hosts, disease spread, prediction systems, and response strategies. The coordination center provides outreach and training, data services, including access to data sets, and computing services for disease modeling. The MIDAS network membership is drawn from

hundreds of national and international research groups. Modeling of vector-borne diseases are included among the infectious diseases investigated by the MIDAS network members. *(NIGMS)*

- The COBRE-funded Center for Microbial Pathogenesis and Host Inflammatory Responses (CMPHIR) at the University of Arkansas for Medical Sciences (UAMS) investigates interplays between pathogens and the host immune system. CMPHIR developed project leaders who went on to obtain independent NIH research grants, including one on plague and another on bacteria that cause tick-borne relapsing fever. The projects have led to the discovery of new virulence factors required for pathogens' invasion of their hosts. *(NIGMS)*
- Infectious Disease and Biological Hazards Training is designed to develop and implement training programs to prevent occupational exposure of workers across levels and facilities to infectious agents that cause diseases. The program is part of the NIEHS Worker Training Program. *(NIEHS)*
- Duke Infectious Disease Response Training (DIDRT) program is a five-state consortium funded by NIEHS to provide up-to-date, high-quality, effective, and efficient biosafety and infectious disease response training. The three-year DIDRT Consortium is based out of the Duke University Regional Biocontainment Laboratory, a high-containment research facility constructed by NIAID which provides a contained and secure place to train people to work with infectious materials safely and to perform research on developing drugs, diagnostics, and vaccines against infectious diseases that impact global health. *(NIEHS)*

Workshops

- Vector Control Product Development Pathway: Phase-Dependent Evidence Gathering workshop was organized to address the need to better understand the data requirements for each phase of product testing, including laboratory and pre-field studies (phase 1), small-scale field studies (phase 2), and large-scale field studies (phase 3). *(NIAID)*
- Driving Success in Vector Control Product Development for Public Health: The Critical Roles of Preferred Product Characteristics (PPC) and Target Product Profile (TPP) Documents workshop was to understand the critical role of preferred PPCs and TPPs in the development of vector control products and to provide investigators with hands-on experience in developing these documents. (NIAID)
- Targeting the Parasite within the Vector: Exploring Novel Approaches to Prevent Transmission of Vector-Borne Diseases workshop brought together experts in vector biology, parasitology, and related areas to discuss approaches to interrupt parasite development within the arthropod host and prevent transmission of human vector-borne diseases. *(NIAID)*
- Incorporating Systems Biology to Vector-borne Pathogen Research: current landscape, challenges, and opportunities brought together experts in arthropod vectors/vector-borne diseases and computation -modeling to explore systems biology approaches in both the vertebrate and invertebrate hosts. *(NIAID)*
- Understanding the Interplay of Environmental Stressors, Infectious Disease, and Human Health: A Workshop brought together experts on infectious disease, global public health, toxicology, environmental epidemiology, and science policy to explore the relationship between chemical pollution in the environment and human health. *(NIEHS)*

- Pivotal Interfaces of Environmental Health and Infectious Disease Research to Inform Responses to Outbreaks, Epidemics, and Pandemics investigated how emerging environmental exposures assessment tools could help to identify and monitor critical pathways for exposure to infectious agents, and how advances in climate modeling techniques could be applied to transmission dynamics to provide early warning of disease outbreaks. (NIEHS)
- International Conference on One Medicine One Science (iCOMOS) focused the attention of global researchers in environmental health, ecosystem health, veterinary medicine, food and agriculture science, and policy on the health challenges of the intersections of urban, rural, and wild landscapes. *(NIEHS, NIAID)*

Appendix D: NIH Institute/Center Research Collaborations in Fiscal Years 2019, 2020, and 2021

This report provides the dollar amounts made available by each NIH IC for conducting or supporting research that involves collaboration between that IC and one or more other ICs.

NIH is composed of 27 ICs, each having a distinct mission. Leaders across NIH recognize that scientific progress often comes at the interface of traditional boundaries. As a result, considerable collaborative activity occurs across IC boundaries at every level of NIH operations. Trans-NIH collaborative activities can be found in all disease areas and throughout basic, translational, and clinical research. These collaborations can be formal or informal and can involve sharing materials, specimens, or scientific expertise. Collaborations take place at any or all stages of a research project or program, including development of a concept, initiative, or plan, funding, conduct of the research in intramural laboratories, management and administration of the project, and assessment of results.

NIH research collaborations across ICOs represent unique opportunities to build on the scientific expertise, sophisticated technologies, infrastructure, and knowledge base of individual ICs and to apply this wealth of information and resources to addressing a wide range of diseases and health conditions. These collaborations produce multidisciplinary and multifaceted approaches to critical scientific questions and lead to special initiatives and innovative programs for the discovery, development, and testing of strategies to diagnose, prevent, and treat a wide range of health conditions. Inter-IC collaborations also enable the leveraging of crucial resources to ensure precious research dollars are used effectively and efficiently to improve the public health of all Americans.

For full information about FY 2019-2021 NIH Institute/ Center Research collaborations, see the NIH Collaborations report:
https://dpcpsi.nih.gov/sites/default/files/Report_NIH%20IC%20Research%20Collaborations_FY19-FY21_final.pdf

For previous reports, see: https://dpcpsi.nih.gov/collaboration/reports

Appendix E: Research Training and Graduate Medical Education Data

Table 7. NRSA and NLM Research Training Programs: Number of Ph.D. Recipients by Field of Study[2184]

Field of Study		Fiscal Year of PhD		
Major and Minor Category	Description	2018	2019	2020
Life sciences	**Overall**	**2,833**	**2,755**	**2,578**
Agricultural sciences and natural resources	Subtotal	13	8	8
Agricultural sciences and natural resources	Animal Nutrition	0	0	1
Agricultural sciences and natural resources	Animal Science, Poultry (or Avian)	0	1	1
Agricultural sciences and natural resources	Animal Science, Other	2	1	1
Agricultural sciences and natural resources	Environmental Science	2	3	2
Agricultural sciences and natural resources	Fishing & Fisheries Sciences/Management	1	0	0
Agricultural sciences and natural resources	Food Science	4	0	0
Agricultural sciences and natural resources	Food Science & Technology, Other	0	1	1
Agricultural sciences and natural resources	Natural Resource/Environmental Economics	1	0	0
Agricultural sciences and natural resources	Plant Pathology/Phytopathology	0	1	1
Agricultural sciences and natural resources	Plant Sciences, Other	2	1	1
Agricultural sciences and natural resources	Soil Chemistry/Microbiology	1	0	0
Biological and biomedical sciences	Subtotal	2,570	2,489	2,316
Biological and biomedical sciences	Anatomy	0	0	2
Biological and biomedical sciences	Bacteriology	3	5	4
Biological and biomedical sciences	Biochemistry	222	201	159
Biological and biomedical sciences	Bioinformatics	44	56	39
Biological and biomedical sciences	Biomedical Sciences	135	112	124
Biological and biomedical sciences	Biometrics & Biostatistics	38	52	27
Biological and biomedical sciences	Biophysics	58	61	57
Biological and biomedical sciences	Biotechnology	5	1	1
Biological and biomedical sciences	Botany/Plant Biology	4	7	2
Biological and biomedical sciences	Cancer Biology	133	132	121
Biological and biomedical sciences	Cell/Cellular Biology & Histology	75	72	58
Biological and biomedical sciences	Computational Biology	42	47	38
Biological and biomedical sciences	Developmental Biology/Embryology	55	42	44
Biological and biomedical sciences	Ecology	7	4	2
Biological and biomedical sciences	Endocrinology	11	2	5
Biological and biomedical sciences	Entomology	0	1	0
Biological and biomedical sciences	Environmental Toxicology	9	17	12
Biological and biomedical sciences	Epidemiology	118	80	77
Biological and biomedical sciences	Evolutionary Biology	12	13	11
Biological and biomedical sciences	Genetics/Genomics, Human & Animal	148	134	149
Biological and biomedical sciences	Immunology	211	185	183
Biological and biomedical sciences	Microbiology	125	101	121

[2184]Data drawn from IMPAC II Current Files and Doctorate Records File as of 8/11/2022 and are subject to change.

Field of Study		Fiscal Year of PhD		
Major and Minor Category	Description	2018	2019	2020
Biological and biomedical sciences	Molecular Biology	171	194	180
Biological and biomedical sciences	Molecular Medicine	23	18	13
Biological and biomedical sciences	Neurosciences & Neurobiology	455	456	407
Biological and biomedical sciences	Nutrition Sciences	30	39	31
Biological and biomedical sciences	Parasitology	5	6	2
Biological and biomedical sciences	Pathology, Human & Animal	28	15	27
Biological and biomedical sciences	Pharmacology, Human & Animal	81	82	86
Biological and biomedical sciences	Physiology, Human & Animal	58	63	47
Biological and biomedical sciences	Plant Genetics	7	5	2
Biological and biomedical sciences	Structural Biology	15	21	19
Biological and biomedical sciences	Toxicology	45	31	28
Biological and biomedical sciences	Virology	46	57	46
Biological and biomedical sciences	Biology/Biomedical Sciences, General	136	150	163
Biological and biomedical sciences	Biology/Biomedical Sciences, Other	15	27	29
Health sciences	Subtotal	250	258	254
Health sciences	Environmental Health	14	15	13
Health sciences	Gerontology	4	4	3
Health sciences	Health & Behavior	5	14	9
Health sciences	Health Services Research	10	20	12
Health sciences	Kinesiology/Exercise Physiology	14	15	16
Health sciences	Medical Physics/Radiological Science	13	10	11
Health sciences	Nursing Science	56	50	56
Health sciences	Oral Biology/Oral Pathology	8	3	8
Health sciences	Pharmaceutical Sciences	20	23	30
Health sciences	Public Health	52	54	50
Health sciences	Rehabilitation/Therapeutic Services	7	7	5
Health sciences	Speech-Language Pathology & Audiology	16	12	15
Health sciences	Veterinary Sciences	10	10	6
Health sciences	Health Sciences, General	4	5	5
Health sciences	Health Sciences, Other	17	16	15
Physical sciences and earth sciences	**Overall**	**179**	**158**	**153**
Chemistry	Subtotal	147	136	124
Chemistry	Analytical Chemistry	10	14	10
Chemistry	Chemical Biology	51	45	34
Chemistry	Inorganic Chemistry	5	6	4
Chemistry	Medicinal Chemistry	14	17	14
Chemistry	Organic Chemistry	24	26	21
Chemistry	Physical Chemistry	13	4	7
Chemistry	Polymer Chemistry	2	1	0
Chemistry	Theoretical Chemistry	1	3	2
Chemistry	Chemistry, General	20	10	26
Chemistry	Chemistry, Other	7	10	6
Geosciences, atmospheric, and ocean sciences	Subtotal	5	5	1
Geosciences, atmospheric, and ocean sciences	Atmospheric Chemistry & Climatology	2	0	0

Field of Study		Fiscal Year of PhD		
Major and Minor Category	Description	2018	2019	2020
Geosciences, atmospheric, and ocean sciences	Geology	0	1	0
Geosciences, atmospheric, and ocean sciences	Paleontology	0	0	1
Geosciences, atmospheric, and ocean sciences	Geological & Earth Sciences, Other	1	0	0
Geosciences, atmospheric, and ocean sciences	Hydrology & Water Resources	0	1	0
Geosciences, atmospheric, and ocean sciences	Marine Biology & Biological Oceanography	1	2	0
Geosciences, atmospheric, and ocean sciences	Marine Sciences	1	1	0
Physics and astronomy	Subtotal	27	17	28
Physics and astronomy	Astrophysics	0	1	1
Physics and astronomy	Acoustics	1	0	1
Physics and astronomy	Applied Physics	4	0	1
Physics and astronomy	Atomic/Molecular/Chemical Physics	0	0	1
Physics and astronomy	Biophysics	13	8	14
Physics and astronomy	Condensed Matter/Low Temperature Physics	1	2	0
Physics and astronomy	Nuclear Physics	1	2	0
Physics and astronomy	Optics/Photonics	4	2	1
Physics and astronomy	Polymer Physics	0	0	1
Physics and astronomy	Physics, General	2	2	7
Physics and astronomy	Physics, Other	1	0	1
Mathematics and computer sciences	**Overall**	**31**	**24**	**23**
Computer and information sciences	Subtotal	10	7	6
Computer and information sciences	Computer Science	8	5	6
Computer and information sciences	Information Science & Systems	1	0	0
Computer and information sciences	Computer & Information Sciences, General	1	2	0
Mathematics and statistics	Subtotal	21	17	17
Mathematics and statistics	Applied Mathematics	4	4	6
Mathematics and statistics	Statistics	12	9	6
Mathematics and statistics	Mathematics/Statistics, General	5	3	5
Mathematics and statistics	Mathematics/Statistics, Other	0	1	0
Psychology and social sciences	**Overall**	**290**	**320**	**310**
Psychology	Subtotal	226	263	242
Psychology	Behavioral Analysis	1	2	1
Psychology	Clinical Psychology	97	125	118
Psychology	Cognitive Neuroscience	37	32	34
Psychology	Cognitive Psychology & Psycholinguistics	9	14	7
Psychology	Community Psychology	1	2	0
Psychology	Counseling	4	3	0
Psychology	Developmental & Child Psychology	12	18	18
Psychology	Educational Psychology	0	1	1
Psychology	Experimental Psychology	7	17	8
Psychology	Health & Medical Psychology	5	5	9

Field of Study		Fiscal Year of PhD		
Major and Minor Category	Description	2018	2019	2020
Psychology	Human Development & Family Studies	13	8	6
Psychology	Industrial & Organizational Psychology	1	1	0
Psychology	Marriage and Family Therapy/Counseling	0	0	1
Psychology	Neuropsychology/Physiological Psychology	6	5	6
Psychology	Personality Psychology	0	3	0
Psychology	Psychometrics & Quantitative Psychology	1	3	1
Psychology	School Psychology	1	1	1
Psychology	Social Psychology	9	8	12
Psychology	Psychology, General	13	10	14
Psychology	Psychology, Other	9	5	5
Social sciences	Subtotal	64	57	68
Social sciences	Anthropology, Cultural	3	3	4
Social sciences	Anthropology, General	1	0	0
Social sciences	Anthropology, Physical and Biological	3	3	3
Social sciences	Economics	8	7	14
Social sciences	Sociology	29	25	19
Social sciences	Area/Ethnic/Cultural Studies	1	0	0
Social sciences	Criminal Justice & Corrections	1	0	1
Social sciences	Criminology	1	1	0
Social sciences	Demography/Population Studies	6	3	5
Social sciences	Geography	2	1	2
Social sciences	Gerontology	0	2	2
Social sciences	Health Policy Analysis	5	9	11
Social sciences	Linguistics	1	0	3
Social sciences	Public Policy Analysis	2	1	3
Social sciences	Urban/City, Community, & Regional Planning	0	0	1
Social sciences	Social Sciences, Other	1	2	0
Engineering	**Overall**	281	254	245
Engineering	Subtotal	273	248	234
Engineering	Bioengineering & Biomedical Engineering	229	217	185
Engineering	Chemical Engineering	30	19	28
Engineering	Civil Engineering	1	1	0
Engineering	Electrical, Electronics, & Communications Engineering	1	6	4
Engineering	Materials Science Engineering	8	0	8
Engineering	Mechanical Engineering	4	5	9
Other engineering	Subtotal	8	6	11
Other engineering	Computer Engineering	0	0	1
Other engineering	Engineering Management & Administration	0	1	0
Other engineering	Engineering Science	1	0	1
Other engineering	Environmental/Environmental Health Engineering	4	3	3
Other engineering	Nuclear Engineering	1	0	2
Other engineering	Operations Research	0	0	1
Other engineering	Polymer & Plastics Engineering	0	1	0
Other engineering	Robotics	0	0	2

Field of Study		Fiscal Year of PhD		
Major and Minor Category	Description	2018	2019	2020
Other engineering	Systems Engineering	0	1	0
Other engineering	Engineering, Other	2	0	1
Other Fields	**Overall**	**21**	**27**	**34**
NIH Total	**Grand Total**	**3,635**	**3,538**	**3,343**

Table 8. Demographic Characteristics of NRSA Participants[2185]

Demographic Characteristic	FY 2018	FY 2019	FY 2020	FY 2021
Gender				
Female	54.4%	54.7%	56.0%	57.4%
Male	42.9%	42.4%	41.3%	39.5%
Unknown	2.7%	2.9%	2.7%	3.1%
Withheld	0.0%	0.0%	0.0%	0.0%
Race				
White	63.9%	63.8%	63.8%	62.7%
Asian	16.3%	16.2%	16.1%	16.0%
Black or African American	7.2%	7.0%	7.5%	8.3%
American Indian or Alaska Native	0.6%	0.6%	0.7%	0.8%
Native Hawaiian or Other Pacific Islander	0.2%	0.2%	0.2%	0.2%
Person Reporting More Than 1 Race	4.7%	5.4%	5.4%	5.5%
Withheld	7.0%	6.8%	6.2%	5.9%
Unknown	0.1%	0.1%	0.2%	0.6%
Ethnicity				
Hispanic or Latino	12.8%	12.8%	13.3%	14.2%
Not Hispanic or Latino	83.5%	83.5%	83.4%	82.5%
Unknown	0.0%	0.0%	0.0%	0.0%
Withheld	3.7%	3.7%	3.3%	3.3%

[2185] NRSA Training grants are T32, T34, T35, T90, TL1, and TU2. Fellowship grants are F30, F31, F32, and F33. TL4 trainees were included beginning in 2015. FY2018 to FY2021 data were drawn from IMPAC II Current Files and Doctorate Records File as of 8/11/2022 and are subject to change. Race and ethnicity are self-reported.

Table 9. Successfully Completed Residency and Subspecialty Training by Academic Year

NIH Clinical Center Program Specialty	Completed		
	2018/2019	2019/2020	2020/2021
Allergy and Immunology	3	3	5
Blood Banking/Transfusion Medicine	3	3	2
Critical Care Medicine	3	3	4
Cytopathology	1	1	1
Endocrinology, Diabetes, and Metabolism	6	5	6
Hematopathology	2	2	2
Hematology-Oncology	10	17	12
Hospice and Palliative Medicine	2	2	2
Infectious Disease	6	4	4
Laboratory Genetics and Genomics	0	0	6
Medical Biochemical Genetics	3	2	3
Medical Genetics and Genomics	4	3	3
Neurological Surgery	1	1	0
Pathology (Anatomic and Clinical)	3	4	3
Clinical Biochemical Genetics	0	0	2
Pediatric Endocrinology	3	3	1
Psychiatry	2	0	2
Reproductive Endocrinology	2	5	3
Rheumatology	1	0	2
Vascular Neurology	5	1	4
Total	**60**	**59**	**67**

Appendix F: Monitoring Adherence to the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research

All NIH-funded studies that meet the NIH definition for clinical research must address plans for the inclusion of women and minorities within the application or proposal. NIH has examined and reported aggregate inclusion enrollment information for its portfolio of NIH-funded clinical research since FY 1994. These reports are one component of the NIH policy on the Inclusion of Women and Minorities as Subjects in Clinical Research.

For each NIH IC that supports clinical research, triennial reports on inclusion have been produced with all NIH enrollment information for FY 2019–2021.

An NIH-wide report covering FY 2019-2020, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, is published as Section V (starting on page 91) of the *Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2019 - 2020.*

For links to the NIH-wide biennial reports, as well as each IC's triennial report, please see https://report.nih.gov/research/inclusion-women-and-minorities-clinical-research#/.

Appendix G: Catalog of Biomedical Information Systems

NIH supports the generation and analysis of substantial quantities of biomedical research data. Storing, managing, standardizing, and publishing the vast amounts of data produced by biomedical research is critical to the NIH mission. NIH has a long tradition of making available to the public the results of research it supports and conducts, including publications and scientific data, and supports many repositories for sharing biomedical data. In an effort to provide biomedical research data more effectively and comprehensively, the NIH-wide BioMedical Informatics Coordinating Committee (BMIC) maintains a list of NIH-supported data repositories[2186] that can be found here: https://www.nlm.nih.gov/NIHbmic/domain_specific_repositories.html.

To help researchers find, use, and share data more efficiently, the NIH Office of Data Science Strategy[2187] works across NIH to modernize the data repository ecosystem to support the storage and sharing of data and to standardize data and adopt CDEs.

NIH exemplifies and promotes the highest level of public accountability and transparency. To that end, the Research Portfolio Online Reporting Tools (RePORT)[2188] provides access to reports, data, and analyses of NIH research activities, including information on NIH expenditures and the results of NIH supported research.

One of the tools available on the RePORT website is the RePORTER[2189] (RePORT Expenditures and Results) module. RePORTER is an electronic tool that allows users to search a repository of both intramural and extramural NIH-funded research projects and access publications and patents resulting from NIH funding.

The RePORT website also contains other tools that provide access to reports and summary statistics on NIH funding and the organizations and people involved in NIH research and training. One of these tools is the NIH Data Book,[2190] which summarizes the most commonly asked questions about the NIH budget and extramural programs. Another tool is called Awards by Location,[2191] which summarizes NIH awards for a particular fiscal year by the location and organization of the awardees.

[2186] https://www.nlm.nih.gov/NIHbmic/index.html
[2187] https://datascience.nih.gov/data-ecosystem
[2188] https://report.nih.gov/
[2189] https://reporter.nih.gov/
[2190] https://report.nih.gov/nihdatabook/
[2191] https://report.nih.gov/award/index.cfm

Appendix H: Actions Undertaken to Carry Out Scientific Frameworks on Recalcitrant Cancer

Update on Progress including PDAC and SCLC Activities, FY 2019–2021

As required by the *Recalcitrant Cancer Research Act (RCRA) of 2012*, the NCI submitted a report to Congress in June 2020, six years after initial development of two scientific frameworks. The report discussed how NCI developed and implemented scientific frameworks for PDAC and small cell lung cancer (SCLC). The frameworks were adopted by NCI's Clinical Trials and Translational Research Advisory Committee (CTAC) and informed by the assessments of the scientific and clinical leaders who participated in CTAC working groups. The frameworks were finalized in 2014 and reviewed in 2019.[2192] These frameworks were developed during times of emerging and important discoveries for these tumor types and for cancer research overall.

Decades of research investments made prior to RCRA by NCI, other NIH institutes and centers, and other research funders, spurred insights into the biology of PDAC and SCLC and new prevention, detection, and treatment approaches. New initiatives in PDAC and SCLC catalyzed by the recent scientific frameworks are ongoing and building on these advances. These include research on the biology of these cancers and translational studies to develop new ways to detect, diagnosis, and treat them. Several of the initiatives have already been reissued to support continued research commitments. NCI supports additional research through investigator-initiated grants and clinical trials and by investing in a broad range of research, extending from basic, to translational and clinical research, to population science.

To address the PDAC framework priorities, NCI leveraged existing research efforts, including NCI's Early Detection Research Network (EDRN), the NCI RAS Initiative, and the RAS Synthetic Lethality Network. NCI formed three new programs: PDAC as it relates to immunotherapy,[2193] early detection,[2194] and diabetes and pancreatitis (in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases),[2195] which was reissued in 2019. Between FY 2019 and 2021, there were 20 active NCI clinical trials for patients with pancreatic adenocarcinoma. In 2019-2021, five awards[2196] and one resource center[2197] were issued in response to two PDAC Consortium RFAs. NCI has maintained support for Specialized Programs of Research Excellence (SPOREs) supporting research on pancreatic cancer[2198] and two GI cancer SPOREs that have a pancreatic cancer[2199] and PDAC focus.[2200]

[2192] https://deainfo.nci.nih.gov/advisory/ctac/workgroup/ctacsupmat.htm
[2193] https://pacmen.org/
[2194] https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection-consortium
[2195] https://www.dmscro.org/cpdpc/index.html
[2196] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-015.html
[2197] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-016.html
[2198] https://trp.cancer.gov/spores/pancreatic.htm
[2199] https://trp.cancer.gov/spores/abstracts/johnshopkins_gi.htm
[2200] https://trp.cancer.gov/spores/abstracts/mdanderson_gi.htm

Some new research supported through the framework initiatives is in the early stages and will come to fruition in the coming years. Researchers have made significant scientific progress in understanding the biology and natural history of PDAC due to research investments by NCI and other research funders. Recent results are providing new avenues for treatment and detection approaches. Progress is described in more detail in the 2019 Progress in PDAC Research working group report.[2201]

To address the SCLC framework priorities, NCI is supporting a SCLC Consortium, with funding mechanisms for research projects and a coordinating center addressing all five framework initiatives. From 2019–2021, NCI has supported 19 research projects and one coordinating center; there are currently six active SCLC Consortium projects. Some research projects are in the early stages, and it is anticipated that the clinical impact of this research will become evident in the future. In 2019, NCI reissued the funding opportunity announcement focused on new therapy and drug resistance projects and extended the scope to research in SCLC biology.[2202] From 2019–2021, there were 49 active SCLC clinical trials.

Below are PDAC and SCLC funding announcements from FY 2019–2021; the table at the end of this appendix contains a full list of all NIH-supported PDAC and SCLC research projects for FY 2019–2021.

Funding Announcements related to Small-Cell Lung Cancer released in FY 2019–2021:

1. PAR-19-361 (Posted Aug 2019, opened Oct 2019): Small Cell Lung Cancer (SCLC) Consortium: Biology, Therapy and Resistance (U01 Clinical Trial Not Allowed)[2203]
2. PAR-21-346 (posted Sept 2021, opened Oct 2021): Limited Competition: Coordinating Center (CC) for the Small Cell Lung Cancer (SCLC) Consortium (U24 Clinical Trial Not Allowed)[2204]

Funding Announcements related to Pancreatic Ductal Adenocarcinoma released in FY 2019–2021:

1. RFA-CA-21-041: Pancreatic Ductal Adenocarcinoma (PDAC) Stromal Reprogramming Consortium (PSRC) (U01 Clinical Trial Not Allowed)[2205]
2. RFA-CA-21-042: Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium Coordinating and Data Management Center (PSRC CDMC) (U24 Clinical Trial Not Allowed)[2206]
3. PAR-21-334: Pancreatic Cancer Detection Consortium: Research Units (U01 Clinical Trial Optional)[2207]
4. PAR-21-335: Pancreatic Cancer Detection Consortium: Management and Data Coordination Unit (U24 Clinical Trial Not Allowed)[2208]

[2201] https://deainfo.nci.nih.gov/advisory/ctac/workgroup/PDAC/WGreport2019.pdf
[2202] https://grants.nih.gov/grants/guide/pa-files/PAR-19-361.html
[2203] https://grants.nih.gov/grants/guide/pa-files/PAR-19-361.html
[2204] https://grants.nih.gov/grants/guide/pa-files/PAR-21-346.html
[2205] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-041.html
[2206] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-042.html
[2207] https://grants.nih.gov/grants/guide/pa-files/PAR-21-334.html
[2208] https://grants.nih.gov/grants/guide/pa-files/PAR-21-335.html

FY 2019, 2020, and 2021 NIH Projects Related to PDAC

Table 10: FY 2019, 2020, and 2021 NIH Projects Related to PDAC

Project Number	Title	Principal investigator(s)	Institution
DP2CA271386	Innovations and mechanisms in tumor subcellular metabolism	Monther Abu Remaileh	Stanford University
DP5OD026427	Immune Activating CAR-Modified Antigen Presenting Cells	Carl J. Deselm	Washington University in St. Louis
DP5OD031864	Cellular phenotypic heterogeneity and resistance to radiotherapy in pancreatic adenocarcinoma	Kenneth L Pitter	The Ohio State University
F30CA192819	A differentiation-based mechanism limiting pancreatic tumor initiation	Nathan M Krah	University of Utah
F30CA196040	Structural basis of chemokine receptor signaling in tumor progression	Andrew B Kleist	Medical College of Wisconsin
F30CA200240	Role of Nix in pancreatic ductal adenocarcinoma	Brinda Alagesan	Stony Brook University
F30CA203238	Mechanisms of Escape from TGF? Tumor Suppression in the Pancreas	Yun-Han Huang	Cornell University
F30CA210587	Mechanism behind CCL21/CCR7-mediated pancreatic cancer progression	Natasha A Moussouras	Medical College of Wisconsin
F30CA213745	The Role of Leukocytes in the Hypothalamus in Cancer Cachexia	Kevin G Burfeind	Oregon Health & Science University
F30CA213883	Identifying novel effectors of oncogenic Kras in pancreatic cells via proximity labelling	Derek K Cheng	Stony Brook University
F30CA213916	FOLFOX-induced kinome reprogramming in pancreatic cancer tumor xenografts	Matthew Lipner	University of North Carolina at Chapel Hill
F30CA216998	The Role of ITIH5 in Suppressing Pancreatic Cancer Metastasis	Eric Young	University of Kansas Medical Center
F30CA220680	Physiological Role of Dynamin-Related Protein 1 in Pancreatic Ductal Adenocarcinoma	Sarbajeet Nagdas	University of Virginia
F30CA220843	Development of a novel Antibody Drug Conjugate for the treatment of pancreatic cancer	Christopher M Gromisch	Boston University

Project Number	Title	Principal investigator(s)	Institution
F30CA224970	Investigating the role of C1-INH in pancreatic ductal adenocarcinoma progression	Salina Yuan	University of Pennsylvania
F30CA225117	CXCR3 in Pancreatic Cancer Progression and Metastasis	Andrew C Cannon	University of Nebraska Medical Center
F30CA228258	The Role of Mutant p53 in Regulating T-cell Immune Evasion in Pancreatic Adenocarcinoma and Other Cancers	Deborah A Silverman	The University of Texas MD Anderson Cancer Center
F30CA239441	The Potential Role of Firboblast Activation Protein as a Natural Killer Cell Immune Checkpoint in Pancreatic Cancer	Allison O'Connell	Georgetown University
F30CA243205	ICOSL Signaling in Macrophages Promotes Anti-Tumor Immunity	Emma Kurz	New York University
F30CA243233	Elucidating the protective role of stromal fibrosis to radiation-induced tumor immunity	Varintra E Krisnawan	Washington University in St. Louis
F30CA243253	Validation of WEE1 kinase as a clinical target in KRAS-mutant pancreatic cancer	John N Diehl	University of North Carolina at Chapel Hill
F30CA254087	Harnessing Dendritic Cells as a Novel Therapy in Pancreatic Ductal Adenocarcinoma	Graham D Hogg	Washington University in St. Louis
F30CA257287	Dysregulation of Liver Macrophages in Pancreatic Cancer	Gregory Beatty; Stacy K Thomas	University of Pennsylvania
F30CA257489	Single Cell Deconvolution of the Pancreatic Tumor Microenvironment	Scott Powers; Ki Hong Oh; Richard Austin Moffitt	Stony Brook University
F30CA260944	Identifying the Role of Tumor Cell Intrinsic DNMT1 in Anti-Tumor Immunity in Pancreatic Ductal Adenocarcinoma	Erin E Hollander; Marisa S Bartolomei; Ben Stanger	University of Pennsylvania
F30CA265134	Characterizing the biochemistry and dynamics of the immune suppressive CXCL12 coat in pancreatic cancer	Douglas Thomas Fearon; Philip A Moresco	Stony Brook University
F30CA265277	Targeting pyrimidine biosynthesis in pancreatic ductal adenocarcinoma	David B Sykes; Nicholas Mullen; Pankaj Kumar Singh	University of Nebraska Medical Center

Project Number	Title	Principal investigator(s)	Institution
F31CA213915	The role of the T cell repertoire in immune checkpoint blockade therapy	Erica Dhuey	University of Pennsylvania
F31CA217070	Role of the hexosamine biosynthesis pathway in pancreatic cancer	Sydney Campbell	University of Pennsylvania
F31CA220750	At the nexus of redox and signaling pathways: regulation of NAD+ kinase	Tanya Schild	Cornell University
F31CA220966	Determining the Role of Discoidin Domain Receptor 2 in the Pathogenesis of Pancreatic Ductal Adenocarcinoma	Jeanine Ruggeri	University of Michigan Ann Arbor
F31CA228223	A combined single cell gene expression and enzyme activity assay to study chemotherapy resistance in pancreatic ductal adenocarcinoma	Brae Petersen	University of North Carolina at Chapel Hill
F31CA232394	Utilizing Nucleic-Acid Scavengers to Ameliorate Inflammation-driven Metastatic Progression in Breast Cancer	Elias Eteshola	Duke University
F31CA232655	Exploring the role of stromal GLI proteins in Pancreatic Ductal Adenocarcinoma	Benjamin Allen; Michael K Scales; Marina Pasca Di Magliano	University of Michigan Ann Arbor
F31CA235997	Bioresponsive MR probes for imaging pancreatic cancer	Megan Kaster	Northwestern University
F31CA236269	Calcium-signaling induced epithelial-mesenchymal plasticity in pancreatic cancer	Robert Norgard	University of Pennsylvania
F31CA236332	Novel Molecular Mechanisms Dictating Pancreatic Cancer Metastasis in Tip30-Deficient Kras-Mutant Mice	Imade Imasuen-Williams	Indiana University; Purdue University Indianapolis
F31CA239494	Mechanisms of B cell specific IL-35 expression in cancer	Daniel E Michaud	University of North Carolina at Chapel Hill
F31CA243163	The mechanism of cancer-specific allele selection for K-RAS	Shikha Sheth	Harvard University
F31CA243344	Metabolism of Extracellular Matrix Supports Pancreatic Cancer Growth	Peter Kim	University of Michigan Ann Arbor

Project Number	Title	Principal investigator(s)	Institution
F31CA243469	Mucin Splice Variants in Pancreatic Cancer Diagnosis and Pathogenesis	Christopher M Thompson	University of Nebraska Medical Center
F31CA246901	Single Cell Dissection of Epigenetic and Tumor Ecosystem Dynamics During Pancreatic Cancer Progression	Cassandra Burdziak	Cornell University
F31CA247037	Elucidating Kras-driven immune infiltration and function in pancreatic cancer	Ashley Velez	University of Michigan Ann Arbor
F31CA247076	Determining the role of myeloid cells in establishing the pre-metastatic niche in pancreatic cancer	Howard Crawford; Samantha B Kemp; Marina Pasca Di Magliano	University of Michigan Ann Arbor
F31CA247416	Elucidating fibroblast/immune crosstalk and plasticity in pancreatic ductal adenocarcinoma	Jennifer S Thalappillil	Stony Brook University
F31CA247457	Metabolic interactions in the pancreatic tumor microenvironment	Yatrik Shah; Marina Pasca Di Magliano; Samuel A Kerk; Costas Andreas Lyssiotis; Howard Crawford; Ben Allen	University of Michigan Ann Arbor
F31CA247489	Defining the role of chromatin remodeling complexes in pancreatic cancer stem cells	Lesley P Ferguson	University of California, San Diego
F31CA247527	Mechanistic Insights and Diagnostic Applications for Hypoxia-Induced Vasorin in Pancreatic Cancer	James A Wells; Lisa Kirkemo	University of California, San Francisco
F31CA250135	T cell mechanisms of immunotherapy response in pancreatic ductal adenocarcinoma	Elana J Fertig; Emily Davis; Elizabeth M. Jaffee	Johns Hopkins University
F31CA250353	Synthesis, and Evaluation of Potent and Selective MEK4 Inhibitors as a Targeted Therapeutic for Metastatic Pancreatic Ductal Adenocarcinoma	Ada J Kwong	Northwestern University
F31CA250443	Bacterial Delivery of CXCR7 Nanobodies to Alleviate Immune Suppression in Pancreatic Cancer	Amanda R Decker	New York Presbyterian Hospital

Project Number	Title	Principal investigator(s)	Institution
F31CA250489	The transcriptional and epigenetic landscape of cell fate changes in murine pancreatic cancer initiation and metastasis	Emily Lo; Patrick Cahan; Andrew P Feinberg	Johns Hopkins University
F31CA257224	Identifying targets for combination therapy with FOLFIRINOX and investigating cell polarity loss as a potential driver of invasion in basal-like PDAC	Sandra Zarmer; Jen Jen Yeh; Gaorav Gupta; Naim Rashid	University of North Carolina at Chapel Hill
F31CA257533	Myeloid cell driven immune suppression in pancreatic cancer	Howard Crawford; Marina Pasca Di Magliano; Rosa E Menjivar	University of Michigan Ann Arbor
F31CA260796	Genetic Determinants of Evolutionary Trajectories and Clinical Course in Pancreatic Cancer	Christine Anne Iacobuzio-Donahue; Katelyn Mullen; Sohrab Prakash Shah	Memorial Sloan Kettering Cancer Center
F31CA265166	Inflammation-induced cellular plasticity in pancreatic homeostasis and tumorigenesis	Todd Evans; Rohit Chandwani; David Falvo	Cornell University
F31CA265168	The Role of Oncostatin M in the PDAC tumor microenvironment and macroenvironment	Daenique Jengelley; Michael C. Ostrowski; Andrea Bonetto; Meijing Wang; Jun Wan; Melissa L. Fishel; Teresa A Zimmers	Indiana University; Purdue University Indianapolis
F31CA265173	Differential pathway engagement and the biological consequences of KRAS variants in cancer	Mandar Muzumdar; Yanixa Quinones Aviles; Mark A Lemmon	Yale University
F31DK122633	Investigating the relationship between macrophage ontogeny and function during pancreatitis	Gwendalyn J Randolph; John M Baer; David G Denardo	Washington University in St. Louis
F32CA213810	Understanding metabolic pathways that support redox homeostasis in cancer	Alexander Muir	Massachusetts Institute of Technology
F32CA217033	Epigenetic therapy for pancreatic cancer	Gaoyang Liang	Salk Institute for Biological Studies
F32CA221114	Examination of ceramide signaling in the crosstalk between pancreatic cancer cells and the tumor microenvironment	Audrey Hendley	University of California, San Francisco

Project Number	Title	Principal investigator(s)	Institution
F32CA225040	Proteomic and Genomic Characterizations of FOXP1 in Pancreatic Cancer	Brittany M Bowman	University of North Carolina at Chapel Hill
F32CA232529	Defining the contributions of WT RAS in RAS-mutant lung cancer	Clint A Stalnecker	University of North Carolina at Chapel Hill
F32CA232543	The novel PRMT5-substrate adaptor interface provides a therapeutic target in MTAP null tumors	Kathleen Mulvaney	Broad Institute
F32CA236183	Identifying phosphatidylinositol metabolism vulnerabilities in cancer pathways	Christopher Counter; Seth Zimmerman	Duke University
F32CA239328	Defining the roles of ERK MAPK in driving KRAS-mutant pancreatic cancer growth.	Channing J. Der; Jennifer E Klomp	University of North Carolina at Chapel Hill
F32CA239417	Characterizing and Targeting the Hypoxic T Cell Surfaceome to Promote Immune Function in Cancer	James R Byrnes	University of California, San Francisco
F32CA243290	Elucidating the role of SHOC2 to enhance MEK inhibitor sensitivity in pancreatic cancer	Jason Kwon	Dana-Farber Cancer Institute
F32CA247466	IDH1 is a novel therapeutic target in pancreatic cancer	Ali Vaziri-Gohar	Case Western Reserve University
F32CA247492	Defining and Targeting Malic Enzyme Dependence in Pancreatic Cancer	Charles Burant; Mengrou Shan; Costas Andreas Lyssiotis; Daniel A Beard; David Benner Lombard; Howard Crawford	University of Michigan Ann Arbor
F32CA250144	The Mitochondrial Calcium Uniporter in Pancreatic Cancer Development, Metastasis, and Treatment	Jillian Weissenrieder; J. Kevin Foskett; Ben Stanger	University of Pennsylvania
F32CA250190	Modulating one-carbon metabolism with diet and targeted inhibitors to treat cancer	Matthew J Mcbride	Princeton University
F32CA260118	Effects of GPCR trafficking on the spatiotemporal control of signaling	Emily E Blythe; Mark E Vonzastrow	University of California, San Francisco

Project Number	Title	Principal investigator(s)	Institution
F32CA264906	ST6Gal-1 contributes to pancreatic cancer initiation by promoting pancreatitis-induced acinar to ductal metaplasia	Michael Marciel; Susan L Bellis; Phillip D Smith	University of Alabama at Birmingham
F32CA265042	Elucidating the molecular mechanisms of PRMT5i response and resistance in LUAD and PDAC	Jacqueline A Lees; Pedro N Pozo	Massachusetts Institute of Technology
F32CA265052	The role of sympathetic nerve associated macrophages during pancreatic adenocarcinoma progression	Andrw M Lowy; Jonathan R Weitz	University of California, San Diego
F99CA234962	Pancreatic cancer stem cells: PD2-mediated novel mechanistic link and metabolomic alterations	Saswati Karmakar	University of Nebraska Medical Center
F99CA245822	Identifying Metabolic Vulnerabilities in Pancreatic Cancer	Alec Kimmelman; Mark R Philips; Douglas Biancur	New York University
F99CA253718	Deciphering molecular mechanisms underlying cellular plasticity and metastasis	Emily N Arner	The University of Texas Southwestern Medical Center
F99CA264414	Reprogramming Metabolic Networks in the Tumor Microenvironment	Costas Andreas Lyssiotis; Samuel A Kerk; Yatrik Shah	University of Michigan Ann Arbor
K00CA223043	Defining the barriers to immune surveillance in solid tumors	Samarth Hegde	Icahn School of Medicine at Mount Sinai
K00CA234962	Pancreatic cancer stem cells: PD2-mediated novel mechanistic link and metabolomic alterations	Saswati Karmakar	Stanford University
K00CA245822	Identifying Metabolic Vulnerabilities in Pancreatic Cancer	Ioannis Aifantis; Richard L Possemato; Douglas Biancur	Whitehead Institute for Biomedical Research; New York University
K01CA240533	Training and Research on Mechanisms of Pancreatic Cancer Associated Muscle Wasting and Related Therapies	Christopher Beck; Scott Gerber; Gary R Morrow; Edward M. Schwarz; Gretchen A Meyer; Calvin L Cole; David C Linehan; Robert Dirksen; Ronald W. Wood	University of Rochester

Project Number	Title	Principal investigator(s)	Institution
K05CA134923	Established Investigator Award in Cancer Prevention & Control	James S Goodwin	The University of Texas System
K07CA204201	Video Informed Consent Tools to Improve Care for Patients With Advanced Pancreatic Cancer	Andrea Enzinger	Dana-Farber Cancer Institute
K07CA222159	Obesity and Pancreatic Cancer Progression and Survival	Ana Babic	Dana-Farber Cancer Institute
K08CA201581	Role of Interleukin-22 and Innate Lymphoid Cells in Pancreas Cancer Initiation and Progression	Timothy Frankel	University of Michigan Ann Arbor
K08CA208016	Elucidating KRAS-specific vulnerabilities in pancreatic cancer	Mandar Muzumdar	Yale University
K08CA218420	Functional interrogation of epigenetic vulnerabilities in KRAS-mutant pancreatic cancer	Andrew J Aguirre	Dana-Farber Cancer Institute
K08CA218690	Defining diverse roles of p53 in pancreatic cancer	Michael P Kim	The University of Texas MD Anderson Cancer Center
K08CA230151	Resistance Mechanisms to Combined Trametinib and 4-aminoquinolones in the Inhibition of Pancreatic Cancer	Conan Kinsey	University of Utah
K08CA234222	Linking epigenetic regulation and TGF-? signaling in pancreatic cancer	Jiaqi Shi	University of Michigan Ann Arbor
K08CA241084	Immune Evasion in Pancreatic Cancer	Lynn M. Schuchter; Gregory Beatty; E J Wherry; Mark S Diamond; Robert H Vonderheide	University of Pennsylvania
K08CA241341	Investigating the non-cell autonomous immune effects of mutant p53 in pancreatic cancer	Lukas Edward Dow; Lewis C. Cantley; Manuel Hidalgo; Despina Siolas	Cornell University; New York University
K08CA245188	Hepatic metabolic reprogramming drives pancreatic cancer cachexia	Aaron Grossberg	Oregon Health & Science University
K08CA248473	Cost Effectiveness of Germline Genetic Testing in Pancreatic Cancer	Manuel Hidalgo; Nadine Tung; Mary Linton B Peters; Pari Vijay Pandharipande	Beth Israel Deaconess Medical Center

Project Number	Title	Principal investigator(s)	Institution
K08CA248624	Neoantigen-Targeted Vaccines in Combination with Immune Checkpoint Inhibitors for Pancreatic Cancer	Hao Wang; Elizabeth M. Jaffee; Nilofer Azad; Elana J Fertig; Robert A. Anders; Neeha Zaidi	Johns Hopkins University
K08CA248710	Personalized preclinical models in pancreas cancer: a tractable approach to precision medicine	Richard A Burkhart	Johns Hopkins University
K08CA259456	Targeting the Stroma for Pancreatic Cancer Treatment	Stephen J Pandol; Lei Zheng; Arsen Osipov	Cedars-Sinai Medical Center; Johns Hopkins University
K08DK105326	The Role of NR5A2 in Pancreas Development and Disease	Sahar Nissim	Brigham and Women's Hospital
K08DK122130	Tissue Resident Immune Cells in Human Pancreas	Donna Farber; Stuart P Weisberg	New York Presbyterian Hospital
K12CA090628	Paul Calabresi Program in Clinical/Translational Research at Mayo Clinic	Aminah Jatoi	Mayo Clinic
K22CA226037	Identification of Key Regulators in Pancreatic Cancer Metastasis	Chang-Il Hwang	University of California, Davis
K22CA237620	The role of PP2A B56a in pancreatic tumorigenesis	Brett C Sheppard; Goutham Narla; Craig S Dorrell; Brittany Allen-Petersen; Andrew C Adey; Terry Morgan; Joe W. Gray	Purdue University West Lafayette
K22CA241387	Imaging zinc secretion from the exocrine pancreas for the early diagnosis of pancreatic adenocarcinoma with MRI	Vikram Deshpande; Nabeel Bardeesy; Motaz Qadan; Cristina R. Ferrone; Maria V Clavijo Jordan; Peter D Caravan	Massachusetts General Hospital
K22CA258805	Targeted disruption of the YAP/TAZ/TEAD axis in pancreatic cancer	Behnam Nabet	Fred Hutchinson Cancer Research Center
K99AR071508	The Extracellular Matrix in Muscle Atrophy	Erin Talbert	Medical University of South Carolina
K99CA218891	Targeting malic enzyme 3 as a synthetic lethality target in pancreatic cancer	Prasenjit Dey	The University of Texas MD Anderson Cancer Center

Project Number	Title	Principal investigator(s)	Institution
K99CA226342	Altered mRNA splicing dependent on mutant p53 identifies novel therapeutic vulnerability in pancreatic cancer	Luisa Escobar Hoyos	Memorial Sloan Kettering Cancer Center
K99CA226363	Cellular mechanisms and therapeutic possibilities of inhibiting oncogenic KRAS	Andrew L Wolfe	University of California, San Francisco
K99CA234221	Understanding metabolic heterogeneity in pancreatic cancer	Allison N Lau	Massachusetts Institute of Technology
K99CA241110	Senescence-Associated Secretory Phenotype (SASP) modulation of the tumor microenvironment as a therapeutic strategy for KRAS-driven tumors	Marcus Ruscetti; Charles M Rudin; Joseph C Sun; Christine Anne Iacobuzio-Donahue; Neal Rosen; Scott W Lowe	Memorial Sloan Kettering Cancer Center
K99CA241357	Disrupting macrophage metabolism to reduce immunosuppression and enhance therapy in pancreatic cancer	Marina Pasca Di Magliano; Kerby Shedden; Christopher J Halbrook; Weiping Zou; Charles Burant; Gabriel Nunez; Costas Andreas Lyssiotis	University of Michigan Ann Arbor
K99CA248838	Targeting aspartate biosynthesis in pancreatic tumors	Kayvan R Keshari; Alec Kimmelman; Henrik Molina; Javier Garcia Bermudez; Sohail Tavazoie; Giorgio Ga. Inghirami; Kivanc Birsoy	Rockefeller University
K99CA252009	Function of mesothelial cells in the tumor microenvironment of pancreatic ductal adenocarcinoma	Rana K Gupta; Eric N. Olson; Huocong Huang; Rolf A Brekken	The University of Texas Southwestern Medical Center
K99CA252153	Dissecting the oncogenic and pro-metastatic roles of PTHLH-mediated calcium signaling in pancreatic cancer	Anirban Maitra; Jason R Pitarresi; Richard Kremer; Anil K Rustgi; J. Kevin Foskett; Ben Stanger; Celeste M. Simon; Gregory Beatty	University of Pennsylvania
K99CA252600	Role of Gstt1 in metastatic maintenance and self-renewal in PDA	Christina Ferrer	Massachusetts General Hospital

Project Number	Title	Principal investigator(s)	Institution
K99CA255936	Mechanisms of translational output control in pancreatic cancer	Simone C Hausmann; Yiwen Chen; Helen Piwnica-Worms; Ivan Topisirovic; Michael Kim; Capucine Van Rechem; Pawel Mazur; Huamin Wang; Mark T Bedford	The University of Texas MD Anderson Cancer Center
K99CA256525	Integrating epidemiologic, clinical, genomic and metabolomic profiles to predict pancreatic cancer risk in a multiethnic population	Christopher A Haiman; Brian Huang; David D Conti	University of Southern California
K99CA263154	Investigating Cellular Communication in the Tumor Microenvironment in Pancreatic Cancer	Marina Pasca Di Magliano; Nina G Steele; Benjamin Allen	University of Michigan Ann Arbor
L30CA199584	Searching for Novel Treatments for Pancreatic Cancer with Homologous Recombination Defects	Julia C Carnevale	Loan Repayment Applications
L30CA253874	Stereotactic Body Radiation and Interleukin-12 Therapy for Pancreatic Ductal Adenocarcinoma	Bradley N Mills	Loan Repayment Applications
L30DK118657	Evaluation of a mixed meal test for the diagnosis and characterization of diabetes mellitus secondary to pancreatic cancer and chronic pancreatitis: the DETECT study	Philip A Hart	Loan Repayment Applications
L30DK126090	The Effect of Pancreatic Endotherapy on Quality of Life in Chronic Pancreatitis	Samuel Y Han	Loan Repayment Applications
L30DK130200	Longitudinal Performance of Cell-Free DNA Methylation as a Biomarker of Pancreatic Beta Cell Death	Lisa R Staimez	Loan Repayment Applications
L30TR003006	Characterizing the genetic heterogeneity and microenvironment of pancreatic intraepithelial neoplasia	Alicia M Braxton	Loan Repayment Applications

Project Number	Title	Principal investigator(s)	Institution
L32MD015434	A Safety Trial of Neoadjuvant MEDI9447 (Oleclumab) and MEDI4726 (Durvalumab) in Patients with Surgically Resectable Adenocarcinoma of the Pancreatic Head	Kevin C Soares	Loan Repayment Applications
L40DK130153	Investigating mechanisms of pancreatic beta-cell dysfunction through the characterization of genetic causes of hyperinsulinism	Jennifer M Ikle	Loan Repayment Applications
L60CA253894	Assessing the management and severity of chronic conditions and racial/ethnic differences in pancreatic cancer incidence	Albert J Farias	Loan Repayment Applications
75N91019D00020-0-759102000001-0	Further Testing Of A Multi-Peptide Kras Vaccine For Pancreatic Cancer Prevention	Venkateshwar Chinthalapally	University Of Oklahoma Hlth Sciences Ctr
75N91019D00021-0-759102100003-0	Evaluation Of Real-Time Metabolic Imaging Biomarkers For Detection Of Pancreatic Premalignant Lesions	Powell Brown	University Of Tx Md Anderson Can Ctr
75N91019D00021-P00001-759102000002-0	Task Order: Preclinical Testing Of Cd73 Inhibitors For Pancreatic Cancer Immunoprevention	Powel Brown	University Of Tx Md Anderson Can Ctr
75N91019D00024-P00008-759101900129-4	Repository Services for epidemiology studies	Ethan Dmitrovsky	Leidos Biomedical Research, Inc.
261200800001E-P00149-9999-97	Bridging Interventional Development Gaps (BrIDGs)	David Heimbrook	Leidos Biomedical Research, Inc.
261200800001E-P00156-9999-36	Repository Services for epidemiology studies	David Heimbrook	Leidos Biomedical Research, Inc.
75N91019C00016-0-9999-1	Topic 394 - A versatile radiation-triggered phosphor platform for localized anti-cancer therapy	Rao Papineni	Pact And Health, Llc
N75N91020C00043-0-9999-0	SBIR Phase I Topic 406 - A Prototype Solution To Facilitate Patient Navigation In Support Of Pancreatic Cancer Care	Greg Downing	Gmg Arcdata Llc
P01CA013106	Cold Spring Harbor Laboratory Cancer Research Center	Bruce W. Stillman	Cold Spring Harbor Laboratory

Project Number	Title	Principal investigator(s)	Institution
P01CA084203	Molecular Response and Imaging-based Combination Strategies for Optimal PDT	Tayyaba Hasan	Massachusetts General Hospital
P01CA117969	Genetics and Biology of Pancreatic Ductal Adenocarcinoma	Ronald Anthony Depinho	The University of Texas MD Anderson Cancer Center
P01CA120964	Molecular Pathogenesis of the Hamartoma Syndromes	David J Kwiatkowski	Brigham and Women's Hospital
P01CA203657	Defining RAS isoform- and mutation-specific roles in oncogenesis	Channing J. Der	University of North Carolina at Chapel Hill
P01CA210944	Radiation and checkpoint blockade for cancer immune therapy	Robert H. Vonderheide; Amit Maity; Andy J. Minn, John E. Wherry	University of Pennsylvania
P01CA217797	Exploiting Redox Metabolism Using Pharmacological Ascorbate for Cancer Therapy	Joseph J. Cullen; Douglas R. Spitz	University of Iowa
P01CA217798	Pancreatic Cancer Metastasis	Surinder K Batra	University of Nebraska Medical Center
P01CA233452	Determinants of Liver Metastasis	Shelly Chi-Loo Lu	Cedars-Sinai Medical Center
P01CA236585	Chemoprevention and mechanisms of obesity-promoted pancreatic adenocarcinoma	Guido Erwin Michael Eibl	University of California, Los Angeles
P01CA236778	The role of the macroenvironment in pancreatic cancer-induced cachexia	Denis Guttridge	Medical University of South Carolina
P01CA244114	Pancreatic Cancer Development: Genetic and Immune Regulation	Laura D Attardi; Seung K Kim	Stanford University
P01CA247886	Transforming Human Pancreatic Cancer Into An Immunologic Disease	Elizabeth M. Jaffee	Johns Hopkins University
P01CA254849	Integrated Immune Engineering for Poor Prognosis Cancers	David Andrew Largaespada; David J Odde; David Masopust	University of Minnesota
P20GM109024	Center for Diagnostic and Therapeutic Strategies in Pancreatic Cancer	Sanku Mallik	North Dakota State University
P20GM113132	The Institute for Biomolecular Targeting	Dean R. Madden	Dartmouth College
P20GM121322	Tumor Microenvironment (TME) CoBRE	Paul R. Lockman	West Virginia University

Project Number	Title	Principal investigator(s)	Institution
P20GM130457	COBRE in Digestive & Liver Disease	Stephen A. Duncan	Medical University of South Carolina
P30CA006973	Regional Oncology Research Center	William George Nelson	Johns Hopkins University
P30CA015083	Mayo Comprehensive Cancer Center Grant	Cheryl Lynn Willman	Mayo Clinic Rochester
P30CA015704	The Fred Hutchinson/University of Washington Cancer Consortium Cancer Center Support Grant	Thomas James Lynch	Fred Hutchinson Cancer Research Center
P30CA016087	Perlmutter Cancer Center Support Grant	Benjamin G. Neel	New York University
P30CA016672	CCSG supplement: HOPE/CARE	Peter W. Pisters	The University of Texas MD Anderson Cancer Center
P30CA036727	Fred & Pamela Buffett Cancer Center Support Grant	Kenneth Harvey Cowan	University of Nebraska Medical Center
P30CA051008	Georgetown University Lombardi Comprehensive Cancer Center Support Grant	Louis M. Weiner	Georgetown University
P30CA056036	Translational Research in Cancer	Andrew Chapman	Thomas Jefferson University
P30CA072720	Immune Radiation Response Index (i- RRI) for Immune Cells from Normal and Tumor Microenvironments	Steven K. Libutti	Rutgers, The State University of New Jersey
P41EB024495	Resource for Molecular Imaging Agents in Precision Medicine	Martin Pomper	Johns Hopkins University
P50AA011999	The Southern California Research Center for ALPD and Cirrhosis	Hidekazu Tsukamoto	University of Southern California
P50CA062924	SPORE in Gastrointestinal Cancers	Stanley R. Hamilton	Johns Hopkins University
P50CA127003	SPORE: DF/HCC SPORE in GASTROINTESTINAL CANCER	Adam Joel Bass; Nabeel El-Bardeesy	Dana-Farber Cancer Institute
P50CA196510	Washington University SPORE in Pancreatic Cancer	William G Hawkins	Washington University in St. Louis
P50CA221707	MD Anderson Cancer Center SPORE in Gastrointestinal Cancer	Anirban Maitra; Scott Kopetz	The University of Texas MD Anderson Cancer Center

Project Number	Title	Principal investigator(s)	Institution
P50CA236733	Vanderbilt-Ingram Cancer Center SPORE in Gastrointestinal Cancer	Robert J. Coffey	Vanderbilt University Medical Center
R00AR071508	The Extracellular Matrix in Muscle Atrophy	Erin Talbert	University of Iowa
R00CA188259	Regulation of cancer cell metabolism and growth by the pancreatic tumor stroma	Mara H Sherman	Oregon Health & Science University
R00CA190889	Integrative Analyses to Identify Pancreatic Cancer Susceptibility Genes	Nicholas J Roberts	Johns Hopkins University
R00CA197816	The SMYD3-ERK5 signaling module in pancreatic cancer	Pawel Mazur	The University of Texas MD Anderson Cancer Center
R00CA204725	Exploring Glycobiology and Discovering Biomarkers for Pancreatic Cancer	Dannielle Engle	Salk Institute for Biological Studies
R00CA208032	Deciphering the role of Lin28b in pancreatic cancer to guide therapeutic discovery	Sita Kugel	Fred Hutchinson Cancer Research Center
R00CA218891	Targeting Malic Enzyme 3 as a Synthetic Lethality Target in Pancreatic Cancer	Prasenjit Dey	Roswell Park Cancer Institute
R00CA218892	Uncovering roles of polyunsaturated fatty acids in pancreatic cancer etiology	Lang Wu	University of Hawaii at Manoa
R00CA226342	Altered mRNA splicing dependent on mutant p53 identifies novel therapeutic vulnerability in pancreatic cancer	Luisa Escobar Hoyos	Yale University
R00CA226363	Cellular mechanisms and therapeutic possibilities of inhibiting oncogenic KRAS	Andrew L Wolfe	Hunter College
R00CA241110	Senescence-Associated Secretory Phenotype (SASP) modulation of the tumor microenvironment as a therapeutic strategy for KRAS-driven tumors	Marcus Ruscetti	University of Massachusetts Medical School

Project Number	Title	Principal investigator(s)	Institution
R00CA241357	Disrupting macrophage metabolism to reduce immunosuppression and enhance therapy in pancreatic cancer	Christopher J Halbrook	University of California, Irvine
R01AA024770	A pooling project on alcohol use and risk of cancers with inconsistent prior evidence, with an emphasis in non-smokers	Pietro Ferrari; Stephanie A Smith-Warner	International Agency For Research On Cancer
R01AI058072	Structural Basis for Chemokine Function	Brian F Volkman	Medical College of Wisconsin
R01AR060209	Admin Supplement FoxO signaling and skeletal muscle atrophy	Andrew Judge; Glenn Walter	University of Florida
R01AR072714	NF-kB Regulation of the Muscle Microenvironment in Cancer Cachexia	Denis Guttridge	Medical University of South Carolina
R01CA034610	TGFB-SMAD Signaling in Stem Cell Differentiation and Tumor Suppression	Joan Massague	Memorial Sloan Kettering Cancer Center
R01CA082683	Signal Transduction by Tyrosine Phosphorylation	Tony Hunter	Salk Institute for Biological Studies
R01CA104125	Cytoskeletal Dynamics in Pancreatic Cancer Metastasis	Gina L Razidlo; Mark A. Mc Niven	Mayo Clinic
R01CA111754	Developing new therapeutic strategies for distinct Ras-driven cancers	Karen Cichowski; Andrew J Aguirre	Brigham and Women's Hospital
R01CA112314	Mechanism and Anti-Cancer Activity of SCFA-Hexosamine Analogs	Kevin J Yarema	Johns Hopkins University
R01CA124723	Role of HSP70 in Pancreatic Diseases	Ashok K Saluja	University of Miami
R01CA129105	Cell Growth Signaling in Cancer Development	David M Sabatini	Whitehead Institute for Biomedical Research
R01CA131045	Early Detection Biomarkers in Pancreatic Adenocarcinoma	Diane Simeone	New York University
R01CA136526	Mechanism of Pancreatic Carcinogenesis	Martin E Fernandez-Zapico	Mayo Clinic
R01CA150190	Targeting Pancreatic Cancer Using Peptide Chemistry: From Bench to Bedside	Dale F Mierke; Debabrata Mukhopadhyay	Mayo Clinic

Project Number	Title	Principal investigator(s)	Institution
R01CA151588	Mechanisms of Pancreatic Inflammation, Tissue Repair and Carcinogenesis	Marina Pasca Di Magliano	University of Michigan Ann Arbor
R01CA154451	Ultrasound-enhanced drug penetration for treatment of pancreatic cancer	Joo H Hwang	Stanford University; University of Washington
R01CA154649	The role of entosis in human cancers	Michael H Overholtzer	Memorial Sloan Kettering Cancer Center
R01CA154823	Validation and Fine-Scale Mapping of Pancreatic Cancer Susceptibility Loci (Study)	Alison P Klein	Johns Hopkins University
R01CA155620	RON Receptor in Pancreatic Cancer Biology and Therapy	Andrew Lowy	University of California, San Diego
R01CA160417	Mitophagy in Tumor Microenvironment	Rui Kang; Daolin Tang; Michael T Lotze; Herbert Zeh	The University of Texas Southwestern Medical Center
R01CA161112	Overcoming stromal barriers to therapeutics in pancreas cancer	Sunil Hingorani	Fred Hutchinson Cancer Research Center
R01CA161976	Reprogramming the Tumor Microenvironment in Pancreas Cancer to Enhance Immunotherapy	Nipun Merchant	University of Miami
R01CA163649	Targeting MUC1-Mediated Tumor-Stromal Metabolic Cross-Talk in Pancreatic Cancer	Kamiya Mehla; Peng-Chu B Tu; Pankaj Kumar Singh; Audrey Jane Lazenby; Channabasavaiah B Gurumurthy; Sarah P Thayer; Jordan Hankins; Fang Yu; E P Reddy; Nicholas Woods	University of Nebraska Medical Center
R01CA163764	On the path to the clinic: Lead optimization and pathway analysis of the pancreatic cancer-selective drug conjugate SW V-49	Dirk M Spitzer; William G Hawkins	Washington University in St. Louis
R01CA167291	Exploiting the Ref-1 node in pancreatic cancer: tailoring new pancreatic cancer therapy using multi-targeted combinations	Mark R Kelley; Melissa L. Fishel	Indiana University Purdue University Indianapolis

Project Number	Title	Principal investigator(s)	Institution
R01CA168611	Regulation of Pancreatic Oncogenesis by RIP1 Kinase	Pratip Chattopadhyay; Kwok Kin Wong; George Miller; Deirdre Cohen; Aristotelis Tsirigos; Jeffrey Weber; Cristina Natarajan Hajdu	New York University
R01CA168863	Modulating innate immune cells in the tumor microenvironment of pancreas cancer to enhance anti-tumor immunity	David C Linehan	University of Rochester
R01CA169702	Interrogate the interaction between tumor cells and nerves in the tumor microenvironment of pancreatic cancer	Alex Leo Kolodkin; Lei Zheng; Robert A Anders	Johns Hopkins University
R01CA174294	Multifunctional immunoPET tracers for pancreatic and prostate cancer	Robert E Reiter; Anna Wu	City Of Hope National Medical Center
R01CA174761	Role of acetyl-CoA in linking cancer cell metabolism and epigenetics	Ben Stanger; Nathaniel Snyder; Kathryn E Wellen; Zhiping P Wang	University of Pennsylvania
R01CA176647	Mutant p53 as actionable cancer-specific target	Ute Moll	Stony Brook University
R01CA176828	Using Markers to Improve Pancreatic Cancer Screening	Elliot Fishman; James R. Eshleman; Ihab Kamel; Michael G. Goggins; Marcia Irene I Canto; Alison P Klein; Lori J Sokoll; Jeanne M Clark	Johns Hopkins University
R01CA177670	The Impact of Macrophage Origin on the Pathogenesis and Treatment Resistance of Pancreatic Cancer	David G Denardo	Washington University in St. Louis
R01CA178445	The role of wild-type KRAS in the context of tumor profession and metastasis	Gloria Huei-Ting Su	New York Presbyterian Hospital
R01CA181244	Discovery of Risk Loci and Genomics of Pancreatic Cancer through Exome Sequencing	Chad Huff; Paul Scheet	The University of Texas MD Anderson Cancer Center
R01CA181445	Interrogating the response of the tumor microenvironment to combination immunotherapy using a microfluidic platform	Venu G Pillarisetty; Mark B Headley; Albert Folch; Taran S Gujral	University of Washington

Project Number	Title	Principal investigator(s)	Institution
R01CA182311	High dose radiation therapy to direct immune responses to pancreatic cancer	Marka Crittenden; Brady Bernard; Rom Leidner; Terry R Medler; Michael J Gough	Providence Portland Medical Center
R01CA182495	Discovering Spatial Mechanisms Regulating Metastatic Invadopodia in PDAC	Michael Bouvet; Richard L. Klemke; Andrew Lowy	University of California, San Diego
R01CA182869	The role of DCLK1 in the initiation of pancreatic ductal adenocarcinoma	Courtney W Houchen	University of Oklahoma Health Sciences Center
R01CA183984	A novel miR-198 replacement therapy for pancreatic cancer	Qizhi Yao	Baylor College of Medicine
R01CA186043	Musashi-mediated control of pancreatic cancer growth and progression	Andrew Lowy; Tannishtha Reya	University of California, San Diego
R01CA186338	ZIP4 is a Novel Molecular Target in Human Pancreatic Cancer	Min Li; Martin E Fernandez-Zapico	University of Oklahoma Health Sciences Center
R01CA187923	Novel Strategies to Potentiate a Ras-targeted Oncolytic Herpes Simplex Virus	Xiaoliu Zhang	University of Houston
R01CA188134	Nrf2 Regulation of Ductal Pancreatic Cancer Etiology and Treatment Response	David A Tuveson	Cold Spring Harbor Laboratory
R01CA188252	ROS-targeted therapy for pancreatic cancer	Nouri Neamati	University of Michigan Ann Arbor
R01CA188300	Motion Management of Pancreatic Cancer in MRI-Guided Radiotherapy	Ke Sheng	University of California, Los Angeles
R01CA188654	MR-HIFU induced drug delivery for pancreatic cancer treatment	Donghoon Lee	University of Washington
R01CA189209	Radio-immunotherapy to Target Cancer Stem Cells in Solid Tumor Malignancies	William J Murphy	University of California, Davis
R01CA190717	Alternatively Spliced Tissue Factor and Pathobiology of Pancreatic Cancer	Vladimir Bogdanov	University of Cincinnati
R01CA191191	IDO2 Targeting in Pancreatic Cancer	George Prendergast	Lankenau Institute for Medical Research
R01CA193365	Molecular Imaging of Cachexia in Pancreatic Cancer	Karen M Horton; Zaver M. Bhujwalla	Johns Hopkins University

Project Number	Title	Principal investigator(s)	Institution
R01CA193650	The adaptive kinome in pancreatic cancer	Gary L Johnson; Jen Jen Yeh	University of North Carolina at Chapel Hill
R01CA193887	Targeting Extracellular Matrix-Cancer Stem Cell Interactions In Pancreatic Cancer	William Matsui	The University of Texas at Austin
R01CA193895	Glutaminase Inhibitor Drug Discovery and Nanoparticle-Based Delivery for Pancreatic Cancer Therapy	Anne Le; Justin S. Hanes; Barbara S. Slusher	Johns Hopkins University
R01CA194321	Imaging drug uptake and distribution in chemoradiation therapy of pancreatic cancer	Kenneth H Yu; Nagavarakishore Pillarsetty; Abraham Jing-Ching Wu; John L Humm	Memorial Sloan Kettering Cancer Center
R01CA194941	Suppression of pancreatic tumorigenesis by the PTF1 transcription factor network	Lewis C Murtaugh; Raymond Macdonald	University of Utah
R01CA195473	Repurposing Disulfiram: A Novel Strategy to Help Cancer Patients Regain Muscle	Aminah Jatoi; Martin E Fernandez-Zapico	Mayo Clinic
R01CA195586	Targeted Radiation Therapy for Pancreatic Cancer	Maneesh Jain; Surinder K Batra	University of Nebraska Medical Center
R01CA195651	Clinical Significance of Pancreatic Cancer Differentiation and Dedifferentiation	Huamin Wang	The University of Texas MD Anderson Cancer Center
R01CA196215	Systemic Therapy with Infectivity-Selective Oncolytic Adenovirus for PDAC	Masato Yamamoto	University of Minnesota
R01CA196228	The Role of post-translational activation of Myc in pancreatic cancer	Rosalie Sears	Oregon Health & Science University
R01CA196639	Prevention of solar UV-induced skin cancer by targeting LTA4H	Liang Liu	University of Minnesota
R01CA196941	Novel Signaling Pathways Regulating Pancreatic Cancer Pathogenesis	Huamin Wang	The University of Texas MD Anderson Cancer Center
R01CA197296	Reprogramming the pancreatic tumor microenvironment with immunotherapy	Elizabeth M. Jaffee; Lei Zheng	Johns Hopkins University
R01CA197916	Targeting macrophages for immunotherapy in pancreatic cancer	Gregory Beatty	University of Pennsylvania

Project Number	Title	Principal investigator(s)	Institution
R01CA197999	Development of Quinoxaline Based IKKbeta Inhibitors for Kras Driven Cancers	Amarnath Natarajan	University of Nebraska Medical Center
R01CA198074	Dosage-Dependent Hedgehog Signaling in Pancreatic Cancer	Benjamin Allen; Marina Pasca Di Magliano	University of Michigan Ann Arbor
R01CA198090	Integrated Signaling in Pancreatic Cancer Progression	Robert Scott Bresalier	The University of Texas MD Anderson Cancer Center
R01CA198095	Novel Strategies for Precision T-cell Therapies	Steven C. Almo	Albert Einstein College of Medicine
R01CA198096	Tumor priming sequences combined with novel nanoparticle drug carriers for enhanced therapeutic efficacy in pancreatic cancer: a tripartite USA/Northern Ireland/Republic of Ireland consortium	Chris Scott; Robert M. Straubinger; Martin Clynes; Wen Wee Ma	University at Buffalo, State University of New York
R01CA198128	Exploiting caveolae-dependent albumin endocytosis to optimize therapy in pancreatic cancer	Sergio Corrales Guerro; Terence M Williams	The Ohio State University; City Of Hope National Medical Center
R01CA199064	Purity Independent SIngle Sample Tumor Classifier for Pancreatic Cancer	Stefan Hubert Boeck; Jen Jen Yeh; Naim Rashid; Bert H O Neil; David C Linehan; Eric Collisson; Kevin Greene; Margaret L Gulley; Brian M Wolpin; Jason Merker; Autumn J Mcree	University of North Carolina at Chapel Hill
R01CA199646	Optimizing Ultrasound Enhanced Delivery of Therapeutics	Flemming Forsberg	Thomas Jefferson University
R01CA200572	PKD1 signaling in the initiation of pancreatic cancer	Peter Storz	Mayo Clinic
R01CA200755	Exploring the Role of Mitochondrial Fission in Pancreatic Tumorigenesis	David F. Kashatus	University of Virginia
R01CA201318	The Paradoxical Role of mTORC1 in the Growth of Nutrient-deprived Pancreatic Cancer Cells Harboring Ras Mutations	Craig B. Thompson	Memorial Sloan Kettering Cancer Center

Project Number	Title	Principal investigator(s)	Institution
R01CA202762	Pharmacogenomic and circulating tumor cell approach to individualized treatment of pancreatic cancer	Kenneth H Yu; Brian J Mccarthy	Memorial Sloan Kettering Cancer Center
R01CA202846	Targeted therapy of peritoneal carcinomatosis using theranostic nanoparticles	Hui Mao; Lily Yang; Y A Wang	Emory University
R01CA203108	Prognostic Biomarkers for ZIP4-mediated Cachexia in Pancreatic Cancer	Yi-Ping Li; Min Li	University of Oklahoma Health Sciences Center
R01CA203890	Combined Tumor And Stromal Targeting To Improve Pancreatic Cancer Response To Immunotherapy	David G Denardo	Washington University in St. Louis
R01CA204228	Comprehensive genetic dissection of druggable KRAS targets	Steven D Leach	Dartmouth College
R01CA204969	Uncovering Role of Exosomes in Regulating Pancreatic Cancer Cell Metabolism	Deepak Nagrath	University of Michigan Ann Arbor
R01CA206069	Development of Targeted Nanotechnology Platform for Pancreatic Cancer	Murali M. Yallapu; Sheema Shabir Khan; Meena Jaggi; Nadeem Zafar; Vincent Diego; Subhash Chauhan	The University of Texas Rio Grande Valley; University of Tennessee Health Science Center
R01CA206105	Regulation of Pancreatic Oncogenesis by the Gut Microbiome	Deepak Saxena; Diane Simeone	New York University
R01CA206444	Rac1 GTPase in tumorigenesis and progression of pancreatic cancer	Michel M Ouellette; Surinder K Batra	University of Nebraska Medical Center
R01CA207031	The molecular mechanisms of metabolism reprogramming in mutant Kras/Ink4a-driven pancreatic ductal adenocarcinoma	Paul J Chiao	The University of Texas MD Anderson Cancer Center
R01CA207189	Regulation of Nutrient Stress-Induced Macropinocytosis in Pancreatic Ductal Adenocarcinoma	Cosimo Commisso	Sanford Burnham Prebys Medical Discovery Institute
R01CA207236	Fasting Protects Small Intestinal Stem Cells from Lethal DNA Damage: Mechanistic Insight and Preclinical Translation	Helen Piwnica-Worms	The University of Texas MD Anderson Cancer Center

Project Number	Title	Principal investigator(s)	Institution
R01CA207643	Real-time monitoring of circulating pancreatic tumor cells and clusters	Erica Carpenter	University of Pennsylvania
R01CA208108	MUC16 in Pancreatic Cancer Progression and Metastasis	Prakash Radhakrishnan	University of Nebraska Medical Center
R01CA208205	Reengineering obesity-induced abnormal microenvironment to improve PDAC treatment	Rakesh K Jain; Dai Fukumura	Massachusetts General Hospital
R01CA208253	Enhancing immune therapy in pancreatic cancer by targeting IL-6	Gregory Lesinski	Emory University
R01CA208272	Developing novel combination therapies for pancreatic cancer	Karina J. Yoon	University of Alabama at Birmingham
R01CA208335	Label free microfluidic isolation, characterization and ex vivo expansion of CTCs	Sunitha Nagrath	University of Michigan Ann Arbor
R01CA208401	Protein and proteolytic activity biomarkers of early stage pancreatic cancer	Kenneth H Yu; Paul Tempst	Memorial Sloan Kettering Cancer Center
R01CA208514	Mechanisms of durable antitumor immunity via CD26hiCD4+ T cells	Chrystal M Paulos; Kent Armeson; Hal E. Broxmeyer; Sherine S Chan	Emory University; Medical University of South Carolina
R01CA208517	Determinants of pancreatic cancer and malignant melanoma phenotypes in CDKN2A hereditary kindreds	Hu Li; Gloria M Petersen; Martin E Fernandez-Zapico	Mayo Clinic
R01CA208644	(PQ11) Targeting STING in the context of chemoradiation therapy to overcome poor preexisting immunity in mouse models of pancreatic cancer.	Marka Crittenden	Providence Portland Medical Center
R01CA209798	Investigating the cause of racial/ethnic disparity in pancreatic cancer incidence	Veronica W. Setiawan	University of Southern California
R01CA209886	MRI-Guided Dendritic-Cell-Based Vaccine Immunotherapy for Pancreatic Cancer	Zhuoli Zhang	Northwestern University; University of California, Irvine

Project Number	Title	Principal investigator(s)	Institution
R01CA210192	Targeted Nanotherapy for Pancreatic Cancer	Murali M. Yallapu; Meena Jaggi; Nadeem Zafar; Bilal B Hafeez; Vincent Diego; Subhash Chauhan	The University of Texas Rio Grande Valley; University of Tennessee Health Science Center
R01CA210439	Targeting the Metabolic Basis of Cachexia in Pancreatic Cancer	Pankaj Kumar Singh	University of Nebraska Medical Center
R01CA210553	Image-guided ultrasound therapy and drug delivery in pancreatic cancer	Katherine Ferrara	Stanford University
R01CA210637	Role of PD2/Paf1 in Pancreatic Acinar to Ductal Metaplasia	Moorthy P Ponnusamy; Surinder K Batra	University of Nebraska Medical Center
R01CA211082	Optical imaging of pancreas cancer organoids for drug development and personalized treatment	Melissa Skala	Morgridge Institute for Research
R01CA211087	Noninvasive prediction of tumor response to gemcitabine using MRI	Guanshu Liu	Kennedy Krieger Institute
R01CA211098	Thrombin-dependent mechanisms of pancreatic ductal adenocarcinoma disease	Matthew Flick	University of North Carolina at Chapel Hill
R01CA211176	Defining cell-intrinsic utilization, cofactor balancing, and metabolomic signatures of NAD+ in pancreatic cancer	Sarah H Elsea	Baylor College of Medicine
R01CA211554	First in human study with 18F-avb6-targeting peptide	Julie L. Sutcliffe	University of California, Davis
R01CA211687	Role of nonsense mediated RNA decay in pancreatic cancer	Mark R Philips	New York University
R01CA211878	Common Genetically Altered Pathways as Targets for Therapy in Pancreatic Cancer	Agnieszka Witkiewicz; Erik Knudsen	Roswell Park Cancer Institute
R01CA211927	Reconstituting human pancreatic cancer development for translational research	Seung K Kim	Stanford University
R01CA212086	Optimizing the Treatment of Pancreatic Adenocarcinoma	Chin Hur; Chung Kong	New York Presbyterian Hospital

Project Number	Title	Principal investigator(s)	Institution
R01CA212350	Stroma targeted theranostic nanoparticles for pancreatic cancer	Lacey R Mcnally	University of Oklahoma; University of Oklahoma Health Sciences Center
R01CA212600	Targeting HuR to improve a synthetic lethal therapy for pancreatic cancer	Jonathan Brody	Oregon Health & Science University; Thomas Jefferson University
R01CA213214	Targeting the RNA Exosome for Cancer Therapeutics	Mats Ljungman; Vaibhav Sahai; Nouri Neamati	University of Michigan Ann Arbor
R01CA213233	Exosomes in Cancer Therapy	Raghu Kalluri	The University of Texas MD Anderson Cancer Center
R01CA213278	Reprogramming Tumor Microenvironment by Nanoparticle	Priyabrata Mukherjee	University of Oklahoma Health Sciences Center
R01CA214793	Elucidating and targeting subtype-specific driver in pancreatic cancer	Haoqiang Ying	The University of Texas MD Anderson Cancer Center
R01CA215471	Dectin-1 signaling drives pancreatic oncogenesis by inducing macrophage-mediated adaptive immune suppression	George Miller	New York University
R01CA215498	Functions of the LKB1 tumor suppressor in control in metabolism and epigenetics	Nabeel Bardeesy	Massachusetts General Hospital
R01CA215607	Targeting cysteine import to induce ferroptotic cell death in pancreatic cancer	Kenneth P Olive	New York Presbyterian Hospital
R01CA216853	Metabolic Regulation of Tumor Progression, Metastasis and Chemoresistance by SIRT5/ELK3 signaling in Pancreatic Cancer	Pankaj Kumar Singh	University of Nebraska Medical Center
R01CA216879	Targeted Molecular Imaging of Plectin-1; Bench to bedside and back again	Kimberly A Kelly; Julie L. Sutcliffe	University of California, Davis
R01CA216987	K-Ras sumoylation in cell proliferation and transformation	Wei Dai; Yuan Chen	New York University
R01CA217907	Galpha13 and pancreatic cancer progression	Hidayatullah G Munshi	Northwestern University
R01CA217989	Exosomes as Endocrine Signaling Molecules in Cancer Cachexia	Daniel L Marks	Oregon Health & Science University

Project Number	Title	Principal investigator(s)	Institution
R01CA218382	Isolation and Assessment of Blood-Circulating Cancer Exosomes with LSS and SERS Lab on a Chip Optical Spectroscopic Instrument	Lev T Perelman	Beth Israel Deaconess Medical Center
R01CA218513	Development and application of asymmetric-flow field-flow (AF4) technology in fractionation and characterization of exosome subpopulations and novel nanoveiscles in pancreatic cancer model	David C. Lyden; Haiying Zhang	Cornell University
R01CA219670	Targeting novel therapeutic vulnerabilities in LKB1 mutant tumors	Kwok Kin Wong; Nabeel El-Bardeesy	Massachusetts General Hospital
R01CA220236	Wnt/?-catenin Signaling in Pancreatic Oncogenesis	Anirban Maitra	The University of Texas MD Anderson Cancer Center
R01CA220237	UBAP2, A New Molecule in Pancreatic Cancer Progression	Priyabrata Mukherjee	University of Oklahoma Health Sciences Center
R01CA222049	Histopathologic validation of 89Zr-DFO-HuMab-5B1 PET/CT imaging in CA 19-9 positive pancreatic cancer	Wolfgang Weber; Michael D'Angelica; Neeta Pandit-Taskar; Jason S Lewis	Memorial Sloan Kettering Cancer Center
R01CA222594	The Evolution of PGD addiction in Human Pancreatic Cancer	Christopher V Wright; Oliver Gene Mcdonald	Vanderbilt University Medical Center; University of Miami
R01CA222648	CHARM 2: Chemotherapy for ablation and resolution of mucinous pancreatic cysts: a prospective, randomized, double-blind, multi-center clinical trial	Matthew T. Moyer; John M Dewitt	Pennsylvania State Univ Hershey Med Ctr
R01CA222862	Tailoring Therapy to Pancreatic Cancer Subtypes	Eric Collisson	University of California, San Francisco
R01CA222907	Development and Application of a Porcine Model of Pancreatic Cancer	Mark A Carlson	University of Nebraska Medical Center
R01CA222930	Deregulation of COMPASS complex and enhancer chromatin in pancreatic cancer	Alexandros Tzatsos	George Washington University

Project Number	Title	Principal investigator(s)	Institution
R01CA222969	Targeting Dectin-2 on Tumor-associated Macrophages for the Treatment of Cancer	Edgar Engleman	Stanford University
R01CA223204	Role of Lipocalin 2 in Pancreatic Cancer	Zobeida Cruz-Monserrate	The Ohio State University
R01CA223483	Investigating the metastatic drive in pancreas cancer	Sunil Hingorani	Fred Hutchinson Cancer Research Center
R01CA224306	A novel molecular cross-talk driving pancreatic cancer progression	Ajay Pratap Singh	University of South Alabama
R01CA224763	Profiling signaling activity and gene expression in single, pancreatic adenocarcinoma cells using CE-RNA-Seq	Nancy Lynn Allbritton; David S Lawrence	University of North Carolina at Chapel Hill; University of Washington
R01CA225637	Mechanism of APE1 in DNA damage response	Shan Yan	University of North Carolina at Charlotte
R01CA225955	Exploring Collateral Lethality for Development of Cancer Therapeutics	Ronald Anthony Depinho	The University of Texas MD Anderson Cancer Center
R01CA226279	Biased chemokine receptor signaling in cancer progression	Michael B Dwinell	Medical College of Wisconsin
R01CA226925	Role of ALK4 in Regulating Receptor Trafficking and Pancreatic Cancer Biology	Gerard C Blobe	Duke University
R01CA226983	Directing the metabolic fate of CAR T cells	Carl H June	University of Pennsylvania
R01CA227133	Use of Circulating MicroRNAs for Early Detection and Risk Assessment for Pancreatic Cancer	Veronica W. Setiawan; Xiao-Ou Shu	Vanderbilt University Medical Center
R01CA227517	Translating Intestinal Radioprotection by EGLN Inhibition to Improve Clinical Outcomes in Unresectable Pancreatic Cancer	Cullen Taniguchi	The University of Texas MD Anderson Cancer Center
R01CA227737	BRAVE hydrogels for interrogating cell-matrix interactions in pancreatic desmoplasia	Chien-Chi Lin	Indiana University; Purdue University Indianapolis
R01CA227849	Redox Modification and Targeting of Mutant KRas in Cancer	Kate S Carroll	Scripps Research Institute

Project Number	Title	Principal investigator(s)	Institution
R01CA228406	Targeting immune stroma interactions in pancreatic cancer	Gregory Lesinski; Bassel El-Rayes	Emory University
R01CA228524	Targeting CXCR2 axis in Pancreatic Cancer	Rakesh K Singh; Surinder K Batra	University of Nebraska Medical Center
R01CA228760	Combination therapy with IFN expressing oncolytic adenovirus for pancreatic cancer	Edward W Greeno; Masato Yamamoto; Ryan M Shanley; Jianling Yuan; Julia Davydova; Ingunn Stromnes	University of Minnesota
R01CA229560	Role of ICAM1 in development and progression of pancreatic cancer	Derek Radisky; Peter Storz	Mayo Clinic
R01CA229580	Identifying and Targeting Metabolic Dependencies in the Pancreatic Tumor Microenvironment	Mara H Sherman	Oregon Health & Science University
R01CA229699	Targeting aberrant enhancer landscapes in pancreatic cancer	Christopher Vakoc	Cold Spring Harbor Laboratory
R01CA229803	Molecular Determinants and Therapeutic Consequences of Immune Heterogeneity in Cancer	Ben Stanger; Robert H Vonderheide	University of Pennsylvania
R01CA229875	Studying drug resistance in AML and PDAC using a novel heterotypic 3D organoid model	Anupriya Agarwal; Emek Demir	Oregon Health & Science University
R01CA230277	Development of a New Strategy to Treat Locally Advanced Pancreatic Cancer	Nejat K Egilmez; Scott Gerber; Tanzy Mae Love; Marvin M Doyley; Edith M Lord; Haoming Qiu; David C Linehan	University of Rochester
R01CA230442	PRedictiOn Algorithms for the DeTECTion of Early Stage Pancreatic Cancer (PRO-TECT)	Bechien Wu	Kaiser Permanente
R01CA231052	Counteracting molecular mechanisms of obesity dependent PDAC progression	Michael Vansaun	University of Kansas Medical Center; University of Miami
R01CA232256	An integrated approach to melanoma metastasis and therapy resistance: effects of age-related changes in the ECM and the biomechanics of the skin	Ashani T Weeraratna; Edna Cukierman	Johns Hopkins University

Project Number	Title	Principal investigator(s)	Institution
R01CA235412	Mechanistic Understanding for the Role of Lin28b in Pancreatic Cancer Progression	David Ting; Raul Mostoslavsky; Nabeel El-Bardeesy	Massachusetts General Hospital
R01CA235672	Novel CCR2 PET for Pancreatic Cancer Imaging and Prediction of Response to Standard and CCR2-Targeted Therapy	Farrokh Dehdashti; Kian-Huat Lim; Yongjian Liu	Washington University in St. Louis
R01CA236389	STAT3 is a Critical Regulator of Tumor Cell Plasticity	Brian S Sheridan; Nancy C. Reich; Scott Powers; Richard Moffitt; Alexei Petrenko	Stony Brook University
R01CA236949	Role of SETD5 in Chromatin Regulation and Tumorigenesis	Pawel Mazur	The University of Texas MD Anderson Cancer Center
R01CA236965	Targeting PYK2 for the treatment of PDAC	Jing Hu	University of Pittsburgh
R01CA237037	Developing translationally-relevant genetically engineered mouse models of lung adenocarcinoma for investigations in cancer immunology	Carmen Jane Booth; Nikhil Joshi; Wei Wei; Marie E Robert; James J Farrell; Katerina Politi; Robert J Homer; Susan M Kaech	Yale University
R01CA237250	3D carbon-nanotubes integrated microdevice for extracellular vesicle isolation and in situ sample preparation towards noninvasive pancreatic cancer diagnosis	Nelson Shu-Sang Yee; Jiangang Liao; Siyang Zheng	Carnegie Mellon University; Pennsylvania State University
R01CA237404	Lineage specifiers governing pancreatic cancer growth and molecular subtype	Eric L Snyder	University of Utah
R01CA237569	Intravascular Delivery of Nanoclusters for Treatment of Deep-Seated Cancers with Magnetic Hyperthermia	Khashayar Farsad; Oleh Taratula; Olena Taratula; Pallavi Dhagat	Oregon State University
R01CA237672	Adoptive T Cell Therapy for Pancreatic Cancer	Anirban Maitra; Cassian Yee; Shubham Pant	The University of Texas MD Anderson Cancer Center
R01CA239219	Imaging Acidosis and Immune Therapy in PDAC	Dario Longo; Jason B Fleming; Robert J Gillies; Arig A Ibrahim Hashim; Pedro Enriquez Navas; Shari Pilon-Thomas; Barbara Ann Centeno	Moffitt Cancer Center

Project Number	Title	Principal investigator(s)	Institution
R01CA240484	Exploiting the Twist1 network in cancer cachexia	Azeddine Atfi	Virginia Commonwealth University
R01CA240515	Targeting the DNA damage response in combination with radiation to induce innate immunity and improve immunotherapy efficacy in pancreatic cancer	Meredith Morgan	University of Michigan Ann Arbor
R01CA240603	Identifying Molecular Drivers of Cellular Plasticity in Pancreatic Cancer	Rushika Perera	University of California, San Francisco
R01CA240654	NRF2-dependent redox signaling in pancreatic cancer	Christopher J. Chang; John Chabot; Ola Larsson; Iok In Christine Chio; Hanina Hibshoosh	New York; Presbyterian Hospital
R01CA240814	Type I Interferon Pathway in Pancreatic Adenocarcinoma	Hallgeir Rui; Serge Y Fuchs	University of Pennsylvania
R01CA240818	Targeting NADPH Oxidase for Pancreatic Cancer Prevention and Therapy	Kenneth Reed Shroyer; Weiqin Lu; Wei Hou	Stony Brook University
R01CA241764	Combating Resistance of Pancreatic Cancer with a First-in-Class Dual Targeted PI3K/EGFR Inhibitor	Alnawaz Rehemtulla; Judith Leopold	University of Michigan Ann Arbor
R01CA242003	Use of BCL-xL Proteolysis targeting chimeras to treat pancreatic cancer	Daohong Zhou; Jose G Trevino; Yaxia Yuan; Guangrong Zheng; Jinping Lai; Ji-Hyun Lee	University of Florida
R01CA243577	Murimwa - Targeted inhibition in stromal TGF? activity in pancreatic cancer	Adam Yopp; Rolf A Brekken; Herbert Zeh	The University of Texas Southwestern Medical Center
R01CA244931	Targeting metabolic stress to induce pancreatic tumor cell death	Costas Andreas Lyssiotis	University of Michigan Ann Arbor
R01CA244938	Exploiting Integrin Signaling to Overcome Resistance to Immunotherapy	David Denardo; Vineet Gupta	Washington University in St. Louis
R01CA245005	POLQ Synthetic Lethality in HR-Deficient Pancreatic Adenocarcinoma	Agnel Sfeir; Diane Simeone	New York University

Project Number	Title	Principal investigator(s)	Institution
R01CA245081	Inhibitors of Oxidative Protein Folding For The Treatment of Cancer	Michael C Ostrowski; Nathan Graeme Dolloff; Ernest R Camp; Patrick M Woster; Christopher Davies	Medical University of South Carolina
R01CA247234	Role of Zinc Dependent EMT-Transcription Factors (EMT-TF) in Pancreatic Cancer Metastasis	Kai Ding; Zhibo Yang; Kar-Ming A. Fung; Min Li; Jingxuan Yang	University of Oklahoma Health Sciences Center
R01CA247441	Vascularized tumor explants for drug testing	Dan G Duda; Jeffrey W Clark; Lance Munn; Sassi Slim	Massachusetts General Hospital
R01CA247471	Modulation of Tumor Microenvironment for Improved Therapy of Pancreatic Cancer	Maneesh Jain; Surinder K Batra; Ravi Salgia	University of Nebraska Medical Center
R01CA247516	Metaplastic Tuft Cells in Pancreatic Cancer	Howard Crawford	Henry Ford Health System; University of Michigan Ann Arbor
R01CA247556	Defining the role of macropinocytosis in solid tumor growth and therapeutic resistance	Aimee L Edinger	University of California, Irvine
R01CA247652	Minibeam Radiation Therapy Enhanced Delivery of Nanoparticle Anticancer Agents to Pancreatic Cancer Tumors	Ziqiang Yuan; Autumn J Mcree; Hong Yuan; Andrew Lucas; Edmund C Lattime; Joel E Tepper; William Christopher Zamboni; Steven Libutti; Allison M Deal; Sha X Chang	University of North Carolina at Chapel Hill
R01CA247666	Use of a Nano-Enabled Platform for Pancreatic Cancer Immunotherapy	Andre E Nel; Jeffrey Zink	University of California, Los Angeles
R01CA247763	Targeting tumor and its microenvironment using nanotherapeutics for pancreatic cancer	Benjamin Swanson; Satyanarayana Rachagani; Lynette M Smith; Daryl Murry; Sarah P Thayer; Surya Mallapragada; Surinder K Batra	University of Nebraska Medical Center
R01CA247898	Targeting Epigenomic Regulators at the Replication Fork in PDAC	Angela Mathison; Aron Geurts; Michael T Zimmermann; Gwen Lomberk; Susan Tsai	Medical College of Wisconsin

Project Number	Title	Principal investigator(s)	Institution
R01CA248160	Stromal metabolism promotes therapeutic resistance in pancreatic cancer	Costas Andreas Lyssiotis	University of Michigan Ann Arbor
R01CA248315	Branched chain amino acids and pancreatic cancer	Ben Stanger; Zoltan P Arany; Kathryn E Wellen; Celeste M. Simon	University of Pennsylvania
R01CA248917	Targeting Focal Adhesion Kinase to Improve RT-inducted Tumor Immunity	Hyun Kim; Esther J. Lu; Eugene J Koay; Julie K Schwarz; David G Denardo	Washington University in St. Louis
R01CA249002	Fibroblast Heterogeneity in Pancreatic Cancer	Jonathan Preall; Taehoon Ha; Paul Robson; Alexander Dobin; David A Tuveson	Cold Spring Harbor Laboratory
R01CA249393	Mechanisms of immunotherapy response and resistance in pancreatic ductal adenocarcinoma	Xavier Revelo; Ingunn Stromnes; Kathryn L Schwertfeger; Steven Shen	University of Minnesota
R01CA250173	Endoplasmic Reticulum-to-Mitochondria Calcium Transfer in Pancreatic Cancer Development, Metastasis, and Treatment	Todd W Ridky; Anil K Rustgi; James K Foskett; John T Seykora; Ben Stanger; Benjamin L Prosser; Jillian S Weissenrieder	University of Pennsylvania
R01CA250529	Leveraging Vulnerabilities Induced by STING Activation in Pancreatic Cancer	Caius Gabriel Radu; Timothy Donahue; Thuc Le	University of California, Los Angeles
R01CA250557	Imaging Modulation of Immune Phenotype	Jianghong Rao; Joo H Hwang; Ronald Levy; Katherine Ferrara; Jai Woong Seo; Jamal S Lewis	Stanford University
R01CA250917	Origins and functions of pancreatic cancer-associated fibroblasts	David W. Dawson; Zheng Xia; Sadik Esener; Mara H Sherman	Oregon Health & Science University
R01CA251174	Targeting Lymph Node Dependent Immune Tolerance in Cancer	Andrew Gentles; Edgar Engleman; Ansuman Satpathy	Stanford University
R01CA251405	Targeting Transglutaminase 2 in cancer cachexia	Azeddine Atfi	Virginia Commonwealth University

Project Number	Title	Principal investigator(s)	Institution
R01CA251726	Targeting the autophagy-lysosome system to block pancreatic cancer	Michael P Rape; Rushika Perera; David W Dawson; Grace E Kim; Alec Kimmelman	University of California, San Francisco
R01CA252223	Mechanisms of Epigenetic Plasticity in PDAC	Chunling Yi; Alessandro Gardini	Georgetown University
R01CA252225	Defining metabolic adaptations within the PDAC "arid" tumor microenvironment	Rahul Suresh Shinde; Ben Stanger; Chi Van Dang	The Wistar Institute
R01CA253316	HIFU-immunotherapy in pancreatic cancer	Katherine Ferrara	Stanford University
R01CA254036	Urine and serum biomarkers for early diagnosis and risk assessment of pancreatic cancer	Maneesh Jain; Lynette Smith; Randall E Brand; Anna Lokshin; Sukhwinder Kaur; Jian-Min Yuan; Surinder K Batra	University of Pittsburgh
R01CA254110	Investigation of novel signaling protein in 3D and in vivo PDAC models using second generation Ref-1 inhibitors	Stephen F Konieczny; Teresa A Zimmers; Millie M Georgiadis; James H Wikel; Melissa L. Fishel; Bumsoo Han; Mark R Kelley	Indiana University; Purdue University Indianapolis
R01CA254268	Combining Irreversible Electroporation with Immunotherapy for the Systemic Treatment of Pancreatic Cancer	Aaron M Miller; Andrew Sharabi; Herve Tiriac; Karen Messer; Jing Yang; Dennis Carson; Rebekah White; Tomoko Hayashi; Silke Paust; Stephen Philip Schoenberger; Andrew Lowy; Zbigniew Mikulski; Nikunj Shukla; Thomas J Kipps	University of California, San Diego
R01CA254806	Regulation and Function of Stromal Macropinocytosis in Pancreatic Ductal Adenocarcinoma	Linda M Bradley; David Scott; Cosimo Commisso	Sanford Burnham Prebys Medical Discovery Institute
R01CA255039	Enhancing engineered T cell therapeutic efficacy for the treatment of pancreatic ductal adenocarcinoma	Beau Richard Webber; Ingunn Stromnes; Xavier Revelo; Branden S Moriarity; Steven Shen	University of Minnesota
R01CA255068	PRSS1 Mutation and Pancreatic Cancer Tumorigenesis	Yan Bi; Baoan Ji; Lizhi Zhang; Mark Mcniven	Mayo Clinic

Project Number	Title	Principal investigator(s)	Institution
R01CA255661	Real-time MRI-guided adaptive radiotherapy of unresectable pancreatic cancer	Christopher Crane; Ricardo Otazo; Hebert Alberto Vargas; Neelam Tyagi; Zhigang Zhang; Etienne Lessard; Nevin Bailey; Marsha Reyngold; Grace Tang	Memorial Sloan Kettering Cancer Center
R01CA255670	Mechanistic investigations of microbiome-driven aryl hydrocarbon receptor activity and macrophage function in pancreatic cancer	William Navarre; Grannie O'Kane; Tracy L Mcgaha; Dana Philpott; Devanand Pinto; Steven Gallinger; Trevor Pugh	University Health Network
R01CA256840	Linear energy transfer (LET) dependencies for understanding pancreatic tumor control and relevant molecular endpoints in support of RBE-based heavy-ion radiotherapy	Igor Shuryak; Sally A. Amundson; Guy Y Garty; Kenneth P Olive	New York Presbyterian Hospital
R01CA256969	Optimizing Pancreatic Cancer Management with Next Generation Imaging and Liquid Biopsy	Zhen J Wang; Geoffrey B Johnson; Rondell P Graham; Adam Olshen; Mark J Truty; Eric Collisson; Benjamin Kipp; Ajit Goenka	University of California, San Francisco
R01CA257509	Relative Immunological Effectiveness (RIE) of Carbon Ion Radiation Therapy for Pancreatic Cancer	Michael F Moyers; Xiaodong Wu; Nils Patrik Brodin; Vivek Kumar; Chandan Guha; Yun Sun; Weiguo Hu	Albert Einstein College of Medicine
R01CA258324	Engaging immunosuppressive myeloid cells in the TME for the treatment of pancreatic cancer	Jeffrey V Ravetch; Mikael Karlsson	Rockefeller University
R01CA258372	Role of extracellular matrix proteins and tumor stroma in DNA repair and cancer progression	John M Asara; Laura Selfors; Ralph Scully; Nada Y Kalaany; Senthil Muthuswamy; Taru Muranen	Beth Israel Deaconess Medical Center
R01CA258917	Mitochondrial heterogeneity as the origin of chemoresistance in pancreatic cancer	Andrea Viale; Linghua Wang	The University of Texas MD Anderson Cancer Center
R01CA260249	Dissecting new mechanisms of lysosome quality control in health and disease	Grace E Kim; Rushika Perera; Aurelien Roux; Roberto Zoncu; Costas Andreas Lyssiotis	University of California, San Francisco

Project Number	Title	Principal investigator(s)	Institution
R01CA260340	Addressing Chemoresistance in Pancreatic and Ovarian Cancers: Photodynamic Priming and Repurposing of Tetracyclines using Targeted Photo-Activable Multi-Inhibitor Liposome	Yuju Zhang; Suresh Ambudkar; Dana Roque; Tayyaba Hasan; Huang Chiao Huang	University of Maryland, College Park
R01CA260678	Targeting KRAS and adenosine mediated immunosuppression in pancreatic cancer	David W. Dawson; Paul Boutros; Thuc Le; Antoni Ribas; Julian Whitelegge; Caius Gabriel Radu; Timothy Donahue; David W. Gjertson; Zev A Wainberg	University of California, Los Angeles
R01CA260955	Predicting Pancreatic Ductal Adenocarcinoma (PDAC) Through Artificial Intelligence Analysis of Pre-Diagnostic CT Images	Temel Tirkes; Vahid Yaghmai; Frank H Miller; Srinivas Gaddam; Marcio Diniz; Christie Y Jeon; Touseef Ahmad Qureshi; Debiao Li; Wolfram Goessling; Stewart C Wang; Yasmin Genevieve Hernandez-Barco; Joseph R Pisegna; Stephen Pandol; Ashley Wachsman; James Buxbaum; Damini Dey; Grace L Su	Cedars-Sinai Medical Center
R01CA261251	Stroma penetrating and immune modulating nanoparticles for image-guided therapy of pancreatic cancer	Lei Zhu; Hui Mao; Y. Andrew Wang; Lily Yang	Emory University
R01CA262506	Re-wiring PDAC Tumor Immunity Through Dendritic Cells	Carl J. Deselm; Gregory Beatty; Andrzej Wojcieszynski; Clifford Grant Robinson; Esther J. Lu; Julie K Schwarz; David G Denardo; William G Hawkins; Mark H O'Hara	Washington University in St. Louis
R01CA262580	Repolarizing the Tumor and Metastatic Microenvironments to Treat Patients with Pancreatic Cancer	David C Linehan; Scott Gerber; Nejat K Egilmez; Aram F. Hezel; Haoming Qiu; Marvin M Doyley; Tanzy Mae Love	University of Rochester

Project Number	Title	Principal investigator(s)	Institution
R01CA262822	Role of type 2 immune response in pancreatic cancer tumorigenesis	Scott I Abrams; Jianmin Wang; Jun Qu; Prasenjit Dey; Huamin Wang	Roswell Park Cancer Institute
R01DK052913	Epigenomic Regulation in Pancreatic Cell Growth	Gwen Lomberk; Anirban Maitra; Raul Urrutia	Medical College of Wisconsin
R01DK060694	Networks for functional regulation of pancreatic acinar-ductal metaplasia and epithelial plasticity	Anil K Rustgi	New York Presbyterian Hospital
R01DK061220	Transcriptional Regulators of the Exocrine Pancreatic Phenotype	Lewis C Murtaugh; Raymond Macdonald	The University of Texas Southwestern Medical Center
R01DK070888	Acinar Biology and Pancreatic Disease	Guy E Groblewski	University of Wisconsin Madison
R01DK107767	Omega-3 derived epoxy fatty acids and sEH in pancreatitis-induced carcinogenesis	Guang-Yu Yang	Northwestern University
R01DK110361	The Hippo signaling pathway in pancreatic epithelial cells orchestrate the inflammatory response R01	Pei Wang	The University of Texas Health Science Center at San Antonio
R01DK117459	Magnetic Resonance (MR) Fingerprinting for Quantification of Pancreatic Tumor Microvasculature	Alexander Guimaraes	Oregon Health & Science University
R01DK123079	Unraveling the Role of NADPH Oxidase in Inflammation-associated Pancreatic Diseases	Weiqin Lu	Stony Brook University
R01DK124342	Mechanisms of injury-induced pancreatic neoplasia	Agnieszka Bialkowska	Stony Brook University
R01DK124474	Mechanisms of Pancreatic Fibrosis	Rodger A. Liddle	Duke University
R01EB017270	Chemophototherapy with Porphyrin-phospholipid Liposomes Permeabilized by Red Light	Jonathan F Lovell	University at Buffalo, State University of New York
R01EB020125	Theranostic nanoparticles for detection and treatment of pancreatic cancer	Lacey R Mcnally	Wake Forest Baptist Medical Center; University of Oklahoma Health Sciences Center

Project Number	Title	Principal investigator(s)	Institution
R01EB025990	Deployable Ultrasound Applicators for MRI Guided Thermal Therapy of Pancreatic Cancer	Chris John Diederich	University of California, San Francisco
R01EB026893	Controllable In Vivo Genome Editing for Immune-Checkpoint Blockade in Solid Tumors	Sheng Tong	Rice University; University of Kentucky
R01EB030494	Patient-specific, high-sensitivity spectral CT for assessment of pancreatic cancer	Russell T Shinohara; Amy Perkins; David P Cormode; Ravindra Manjeshwar; Peter O'Dwyer; Joseph W Stayman; Kevin Brown; Nadav Shapira; Mark Rosen; Peter B Noel; Jianan G Gang	University of Pennsylvania
R01EB032337	Surrogate biomarkers for assessing changes in pancreatic cancer tumor microenvironment	Marvin M Doyley; David Dombroski; Brian W. Pogue; Michael G Drage; David C Linehan; Tanzy Love; Petr Bruza; Scott Gerber; Ingolf Sack; Aram F. Hezel	University of Rochester
R01GM066817	The Biochemical Basis for the Mechanics of Cytokinesis	Douglas N Robinson	Johns Hopkins University
R01GM126088	Lipid Regulation of Hypoxia-inducible Factors	Peter J Espenshade	Johns Hopkins University
R01GM138668	Phosphatidylserine acyl chain remodeling regulates KRAS spatial distribution and function on the plasma membrane	Guangwei Du; Alemayehu Gorfe; Ransome Van Der Hoeven; Ilya Levental; Yong Zhou	The University of Texas Health Science Center at Houston
R01GM143329	PR55-alpha controlled PP2A in the regulation of the Hippo/YAP pathway	Nicholas T Woods; Lynette M Smith; Michel M Ouellette; Jixin Dong; Michael A Hollingsworth; Ying Yan; Geoffrey A Talmon	University of Nebraska Medical Center
R01HL147149	mechanism of venous thrombosis in pancreatic cancer	Nigel Mackman	University of North Carolina at Chapel Hill
R03CA216114	IL-15 TRiKES-based specific immunotherapy of TNBC; resistance mechanisms	Daniel A Vallera; Soldano Ferrone	Massachusetts General Hospital

Project Number	Title	Principal investigator(s)	Institution
R03CA223271	Carbidopa as an inhibitor of the TrpT/ID01 functional complex: A novel immunotherapy agent	Shenping Yang; Matthew B Grisham; Yangzom Doma Bhutia; Pushpak Bhattacharjee	Texas Tech University Health Sciences Center
R03CA223619	Predicted lean body mass, fat mass, and risk of lung, pancreatic, colorectal, breast, and prostate cancers	Edward Giovannucci	Harvard University
R03CA223717	Understanding the link between high-fructose intake and pancreatic cancer development	Jelena Todoric	University of California, San Diego
R03CA228007	Porphyromonas gingivalis and Pancreatic Carcinogenesis in Mouse Models	Caroline A Genco	Tufts University
R03CA231766	IL-15 TRiKES-based specific immunotherapy of pancreatic ductal adenocarcinoma	Soldano Ferrone; Cristina R. Ferrone	Massachusetts General Hospital
R03CA235208	The initiation of exosome microRNA signaling in pancreatic cancer cells	Wei-Qun Ding	University of Oklahoma Health Sciences Center
R03CA241971	Epigenetic Regulation of Hemidesmosome Signaling in Pancreatic Cancer	Andrew Liss; Mari Mino-Kenudson; Kasper Lage Hansen	Massachusetts General Hospital
R03CA249401	Combining Immunotherapy with Urolithin A to Improve Pancreatic Cancer Survival	Eli Gilboa; Nagaraj S Nagathihalli; Xi Steven Chen; Eric Wieder; Nipun Merchant	University of Miami
R03CA249542	B7-H3 CAR T cell-based immunotherapy combined with Losartan to counteract desmoplasia for the treatment of Pancreatic Ductal Adenocarcinoma (PDAC)	Soldano Ferrone; Cristina R. Ferrone	Massachusetts General Hospital
R03CA252783	Using the secondary structure (beta-sheet) of exosomal proteins for noninvasive pancreatic cancer detection	Bakhtiyor Rasulev; Rick J Jansen; Dali Sun	North Dakota State University
R03DK122232	The Impacts of NR5A2 Pharmacologic Agonism on Pancreas Development and Disease	Sahar Nissim	Brigham and Women's Hospital
R03TR003639	Nanobody inhibitors of proton-sensing G protein-coupled receptors	Geoffrey A Chang; Chang-Wook Lee; Paul A Insel	University of California, San Diego

Project Number	Title	Principal investigator(s)	Institution
R13AA020691	International Symposium of ALPD and Cirrhosis	Hidekazu Tsukamoto	University of Southern California
R13CA243264	Sixth AACR Special Conference on Pancreatic Cancer: Advances in Science and Clinical Care	Magaret Foti; Dafna Bar-Sagi; Brian M Wolpin; Elizabeth M. Jaffee; Ben Stanger; Luis Diaz	American Association For Cancer Research
R13DK122825	PancreasFest 2019: Team Science for complex Pancreatic Diseases and Pancreatic Cancer: Goals, Milestones and Methods	David Whitcomb	University of Pittsburgh
R13DK130515	PancreasFest 2021	David Whitcomb	University of Pittsburgh
R15CA238864	Rational Oncolytic Virotherapy For Pancreatic Cancer Using Vesicular Stomatitis Virus	Nury Steuerwald; Valery Zurabovich Grdzelishvili; Mitesh Borad	University of North Carolina at Charlotte
R15CA249714	GSTP1 as a therapeutic target for pancreatic cancer	Katie Reindl; Mikhail Y Golovko	North Dakota State University
R21AA026462	Mechanisms of Alcohol Initiation of Chronic Pancreatic Diseases	Raghu Kalluri	The University of Texas MD Anderson Cancer Center
R21CA212827	Single-molecule mechanical detection of protein and microRNA cancer biomarkers	Wesley Philip Wong	Boston Children's Hospital
R21CA216722	Novel Pan-Ralgef Inhibitors To Block Pancreatic Cancer	Geoffrey J Clark	University of Louisville
R21CA218732	PancFit: Do angiogenic biomarkers correlate with improved progression free survival in pancreatic cancer?	Keri L Schadler; An T Ngo-Huang; Matthew Katz	The University of Texas MD Anderson Cancer Center
R21CA218960	Identification of Plasma- and Exosome-Based Protein Biomarkers for Early Detection of Pancreatic Cancer Using SOMAscan Technology	Towia Libermann	Beth Israel Deaconess Medical Center
R21CA219899	PET imaging of the tumor microenvironment for cancer detection	Thaddeus J Wadas	Wake Forest Baptist Medical Center; University of Iowa
R21CA220073	Predicting the diagnosis of pancreatic cancer by leveraging big data	Christie Y Jeon	Cedars-Sinai Medical Center
R21CA223102	Co-targeting PDAC tumor cells and the microenvironment to succeed in EGFR/ErbB2-targeted therapy	Dihua Yu	The University of Texas MD Anderson Cancer Center

Project Number	Title	Principal investigator(s)	Institution
R21CA223304	Accurate Determination of Dose to Mobile Organs at Risk in Hypofractionated Ablative Radiotherapy for Locally Advanced Pancreatic Cancer	Gikas S Mageras	Memorial Sloan Kettering Cancer Center
R21CA223403	A pre-clinical x-ray/optical tomography-guided radiation research platform for pancreatic cancer	Ken K Wang; Phuoc T Tran	Johns Hopkins University; The University of Texas Southwestern Medical Center
R21CA223429	New Strategy for Pancreatic Cancer Therapy	Joyce C Solheim	University of Nebraska Medical Center
R21CA224280	3D biomimetic image-based stromal models of pancreatic cancer for drug screening	Melissa Skala; Paul J Campagnola	University of Wisconsin Madison
R21CA227416	Phospholipase D1 and pancreatic cancer	Edward J Kim; Karen E Matsukuma; Gerardo Guillermo Mackenzie	University of California, Davis
R21CA228187	Targeting asymmetric ciliary signaling in cancer	Erica Golemis	Fox Chase Cancer Center
R21CA230120	Deployable Endoluminal Ultrasound Phased Array for Precision Treatment of Pancreatic Cancer	Chris John Diederich	University of California, San Francisco
R21CA231196	Taste Receptor Family 2 Member 9 as a novel target for imaging Cancer Associated Fibroblasts in pancreatic cancer	Kimberly A Kelly	University of Virginia
R21CA231252	Oncogenic Synapses: cell-cell contacts enabling trogocytic-based metabolic interactions between pancreatic cancer and fibroblastic stromal cells	Edna Cukierman; Igor A. Astsaturov	Fox Chase Cancer Center
R21CA234637	Novel four dimensional magnetic resonance imaging to monitor pancreatic tumor infiltrating blood vessels and tumor response to chemoradiation therapy	Mourad Tighiouart; Zhaoyang Fan; Yi Lao; Nicholas Nissen; Richard Tuli; Wensha Yang; Matthew Weiss; Debiao Li; Rola Saouaf	University of Southern California
R21CA234681	A promising small molecule for pancreatic cancer therapy	Arun K Sharma	Penn State Milton S. Hershey Medical Center

Project Number	Title	Principal investigator(s)	Institution
R21CA234775	Large-scale proteome-wide analysis with high accuracy/precision to guide pancreatic cancer therapy development	Jun Qu; Robert M. Straubinger; Donald Mager	University at Buffalo, State University of New York
R21CA236561	Single Circulating Vesicle Analysis for Early Cancer Detection	Katherine Yang; Ralph Weissleder; Hakho Lee; Carlos Fernandez	Massachusetts General Hospital
R21CA236612	A microfluidic cell culture platform for personalizing pancreatic cancer therapies	Alexander Revzin	Mayo Clinic
R21CA236640	T-cell Biofactories for targeting interstitial fluid pressure	Michael H. Kershaw; Parijat Bhatnagar; Anjana Rao; Calvin J. Kuo; Harold S. Javitz; Lucia Beviglia; George Albert Fisher	SRI International
R21CA238953	Altered Histidine Metabolism in Pancreatic Cancer: A Novel Metabolic Target to Enhance Gemcitabine Efficacy	Robert Powers; Saraswathi Viswanathan; Geoffrey A Talmon; Satyanarayana Rachagani; Surinder K Batra; Lynette M Smith	University of Nebraska Medical Center
R21CA241007	Phase 1 study to test safety and dose of proglumide as an anti-fibrotic agent	Jill P Smith	Georgetown University
R21CA243701	The Macropinosome: Uncovering the Molecular Anatomy of an Oncogene-driven Organelle	Cosimo Commisso	Sanford Burnham Prebys Medical Discovery Institute
R21CA244025	Mitochondrial control of epigenetic reprogramming in pancreatic tumorigenesis	Alessandro Carrer; Rohit Chandwani	Cornell University
R21CA244167	Smoking carcinogen-induced initiation of pancreatic cancer	Peter Storz	Mayo Clinic
R21CA245437	Identify tumor suppressor driver genes of pancreatic ductal adenocarcinoma	Habil Zare; Howard Crawford; Aatur Dilip Singhi; Pei Wang; Francis Sharkey	The University of Texas Health Science Center at San Antonio
R21CA246550	Parametric optimization of ultrasound-mediated immuno-modulation for pancreatic cancer therapy	Yueh Z Lee; Naim Rashid; Gianpietro Dotti; Yuliya Pylayeva-Gupta; Paul A Dayton; Autumn J Mcree	University of North Carolina at Chapel Hill

Project Number	Title	Principal investigator(s)	Institution
R21CA249649	Tumor-permeable nanoparticles for enhanced pancreatic cancer immunochemotherapy	Song Li; Jingjing Sun; Ajay Rana; Binfeng Lu	University of Pittsburgh
R21CA251151	PROTACs for pancreatic cancer therapy	Amarnath Natarajan	University of Nebraska Medical Center
R21CA252156	In situ cancer cell specific synthesis of gold nanoclusters for radiosensitization of pancreatic cancer	Sunil Krishnan; Michael Kim; Konstantin V Sokolov	The University of Texas MD Anderson Cancer Center
R21CA252535	Neoadjuvant Stroma Modification in Pancreatic Cancer	Edna Cukierman; Harry S. Cooper; Efrat Dotan; Elizabeth A. Handorf; Sanjay Reddy; Suraj Peri; Igor A. Astsaturov	Fox Chase Cancer Center
R21CA252585	Targeting Cell Cycle Plasticity in Pancreatic Ductal Adenocarcinoma	Agnieszka K Witkiewicz; Erik Knudsen; Chongmin Huan; Yun Wu	SUNY Downstate Medical Center
R21CA253673	Microbiota pancreas interactions during cancer	Jennifer H Hill; Lewis C Murtaugh; June Louise Round; Ignacio Garrido-Laguna	University of Utah
R21CA255291	Rapid evaluation of immunotherapy regimens in ex vivo human pancreatic tumor slice cultures.	David Jason Bentrem; Hidayatullah G Munshi	Northwestern University
R21CA256409	Mediators of Pancreatic Cancer-Associated Cachexia	Zobeida Cruz-Monserrate; Philip Hart; Christopher C Coss; Martha A Belury	The Ohio State University
R21CA257972	Sex-dependent rescue of cancer cachexia	Chaorong Wu; Erin Talbert; Carlos H.-F. Chan; Jessica Alan Sieren	University of Iowa
R21CA258153	An Inducible Model for Studying Cancer Stem Cells in PDAC	Chunling Yi	Georgetown University
R21CA259240	The role of gut microbe-derived choline metabolites in driving the pro-inflammatory macrophage phenotype and restricting pancreatic cancer	Erica L Carpenter; Rahul Suresh Shinde; Kyle Bittinger; Rugang Zhang; Frederic D Bushman; Qin Liu; David W Speicher; Farokh Dotiwala; Ben Stanger	The Wistar Institute

Project Number	Title	Principal investigator(s)	Institution
R21CA264004	Immunophenotype Integration for Monitoring T Cell Dynamics in Pancreatic Cancers	Alison P Klein; Elizabeth M. Jaffee; Dung Le; Elana J Fertig; Won Jin Ho	Johns Hopkins University
R21CA265400	Domain-Knowledge Informed Deep Learning for Early Detection of Pancreatic Cancer	Chin Hur; Nicholas P Tatonetti; Simon Tavare; Jiheum Park	New York Presbyterian Hospital
R21EB028429	Employing Novel Porcine Models of Orthotopic Pancreatic Cancer to Evaluate Histotripsy Based Tumor Ablation Strategies	Irving Coy Allen	Virginia Tech
R21LM012759	Identification and characterization of interaction atlases in human	Hasan Otu	University of Nebraska Lincoln
R33CA204704	Multiplex FRET Imaging of Kinase-Epigenome Interregulations in Live Cancer Cells	Yingxiao Wang	University of California, San Diego
R33CA206907	Rapid unbiased isolation and in situ RNA analysis of circulating tumor cells using a magnetic micropore-based diagnostic chip	David A Issadore	University of Pennsylvania
R33CA206949	Advanced Development and Validation of 3 Dimensional Spheroid Culture of Primary Cancer Cells using Nano3D Technology	Timothy P Spicer	Scripps Research Institute
R33CA229068	Advanced Development of the MasSpec Pen for Cancer Diagnosis and Surgical Margin Evaluation	James Suliburk; Robert Tibshirani; Livia Schiavinato Eberlin; George Van Buren; Chandandeep Nagi; Stacey Ann Carter	Baylor College of Medicine; The University of Texas at Austin
R35CA197566	Mechanisms governing metastatic dormancy and reactivation	Filippo G Giancotti	New York Presbyterian Hospital; The University of Texas MD Anderson Cancer Center
R35CA197591	Integrative approaches to elucidate p53 transcriptional networks during carcinogenesis	Laura D Attardi	Stanford University
R35CA197627	Breaking the Obesity-Cancer Link: New Targets and Strategies	Stephen D Hursting	University of North Carolina at Chapel Hill

Project Number	Title	Principal investigator(s)	Institution
R35CA197699	Molecular strategies for early detection and targeting of cancer	Daniel Von Hoff; Andrew Lowy; Tannishtha Reya	University of California, San Diego
R35CA197709	New Ways of Targeting K-Ras	Frank P Mccormick	University of California, San Francisco
R35CA209960	Molecular Imaging and Theranostics of Cancer	Zaver M. Bhujwalla	Johns Hopkins University
R35CA210088	The Role of Stem Cells and the Microenvironment in Gastrointestinal Cancers	Tim Wang	New York Presbyterian Hospital
R35CA232113	Targeting undruggable RAS for cancer treatment	Channing J. Der	University of North Carolina at Chapel Hill
R35CA232124	Identifying Metabolic Dependencies of Pancreatic Cancers	Alec Kimmelman	New York University
R35GM131800	Mechanistic Pharmacokinetics and Pharmacodynamics	William Jusko	University at Buffalo, State University of New York
R35HL155657	Tissue factor-dependent coagulation in thrombosis and immune responses	Rafal L Pawlinski; Yohei Hisada; Nigel Mackman; Silvio Antoniak	University of North Carolina at Chapel Hill
R37CA214679	Multi-site Gastrointestinal Cancer Detection by Stool DNA Methylation	John Kisiel	Mayo Clinic
R37CA215427	Clinical Translation of Nuclear Export Inhibitor in Metastatic Pancreatic Cancer	Asfar S Azmi	Wayne State University
R37CA219697	IRAK4 As a Novel Immunotherapeutic Target in Pancreatic Ductal Adenocarcinoma	Kian-Huat Lim	Washington University in St. Louis
R37CA222215	Combined radiation acoustics and ultrasound imaging for real-time guidance in radiotherapy	Issam M El Naqa	Moffitt Cancer Center; University of Michigan Ann Arbor
R37CA227865	Targeting pancreatic cancer's metabolic addiction to HuR	Jordan Winter	Case Western Reserve University
R37CA229417	Spacer Enabled Robust Radiation Therapy (SERRT)	Kai Ding	Johns Hopkins University

Project Number	Title	Principal investigator(s)	Institution
R37CA230786	Function of IL35+ B cells in pancreatic cancer	Benjamin G Vincent; Yuliya Pylayeva-Gupta; Jonathan S Serody; Jen Jen Yeh; Gail Bishop; Naim Rashid	University of North Carolina at Chapel Hill
R37CA234006	Novel Nanomedicine-Based Therapeutic Approach For Treatment of Cancer Cachexia	Gaurav Sahay; Daniel L Marks; Vitaly P Pozharov; Oleh Taratula; Adam Alani; Olena Taratula	Oregon State University
R37CA237384	Dissecting the source and mechanisms of IL-17-mediated modulation of pancreatic tumorigenesis	Florencia Mcallister	The University of Texas MD Anderson Cancer Center
R37CA237421	Intratumoral Metabolic Crosstalk Promotes Therapeutic Resistance in Pancreatic Cancer	Costas Andreas Lyssiotis	University of Michigan Ann Arbor
R37CA240765	Cancer under pressure: Mechanisms of adaptation to compressive stress	Liam J Holt	New York University
R37CA241472	Exploring the epigenetic control of pancreatic cancer subtypes	Chad (Qianchuan) He; Sita Kugel	Fred Hutchinson Cancer Research Center
R37CA242070	Targeting tumor architecture as a novel therapeutic strategy for pancreatic cancer	Matteo Ligorio; Linda Nieman; Martin Joseph Ankrah Aryee; Reto Paul Fiolka; Cristina R. Ferrone; Suntrea Teonta Goudeau Hammer	The University of Texas Southwestern Medical Center
R37CA244911	Targeting stem-like cells and their niche in pancreatic cancer	Michael J Mitchell; Christine Anne Iacobuzio-Donahue; Dana Pe'Er; Tuomas Tammela; Andrea Schietinger	Memorial Sloan Kettering Cancer Center
R37CA249007	Engrailed-1 and Epigenetic Vulnerabilities in Metastatic Pancreatic Cancer	Ed J Kim; Shuai Chen; Chang-Il Hwang	University of California, Davis
R37CA251877	Mechanistic dissection and inhibitor targeting of autophagy in RAS driven cancers	Emanuel F. Petricoin; Valerie Calvert; Kirsten Bryant	University of North Carolina at Chapel Hill
R37CA252305	Regulation of tumor suppression by alpha-ketoglutarate	Lydia W.S. Finley	Memorial Sloan Kettering Cancer Center

Project Number	Title	Principal investigator(s)	Institution
R41CA235842	A dual histone deacetylase and glycogen synthase kinase 3 beta inhibitor for treating pancreatic adenocarcinoma	Michael Stanley Lewis; Stephen Pandol; Mouad Edderkaoui	AVENZOAR PHARMACEUTICALS, INC.
R41CA239853	Advancement of ACXT-3102 for the Treatment of Pancreatic Adenocarcinoma (PDAC)	William G Hawkins; Dirk M Spitzer; Bradley T Keller	ACCURONIX THERAPEUTICS, INC.
R41CA247009	Using Targeted Lipid Nanoparticles to Deliver Chemotherapeutic Agents against Pancreatic Cancer	Jonathan Moreno; Maria Lambros; Mike Nicolaou	DORICPHARMA LLC
R41CA247165	Tumor Stroma Breaking System for Efficient Delivery of Therapeutic Agents	H T Spencer; Lily Yang; Lei Zhu	MIGRA-THERAPEUTICS, LLC
R41CA250892	Modulation of the gut microbiome to enhance efficacy of immunotherapy in pancreatic adenocarcinoma	Satish Sakilam; Malivin Jinal; Deepak Saxena; Xin Li; Xin Li	PERIOMICS CARE, LLC
R41CA254492	Development of a Targeted Radiotherapeuitc for Pancreatic Ductal Adenocarcinoma	Jered C Garrison; Megan Hyun; Craig Johnson; Shana Ann Garrison; Maneesh Jain	ADDUCTNE, LLC
R41CA265512	A novel monobody-drug conjugate to treat mutant KRas pancreatic cancer.	Craig P Ramirez; Shohei Koide; Dafna Bar-Sagi; Andrew David Hauser; Nathan Beals	TEZCAT LABORATORIES LLC
R41CA265619	The use of tMUC1/CD3 bispecific antibody to control pancreatic ductal adenocarcinoma	Ryan Hallett; Ru Zhou; Pinku Mukherjee	OncoTab (United States)
R41CA265624	Bispecific T cell engagers for the treatment of pancreatic ductal adenocarcinoma	Michael C. Ostrowski; Nathan Graeme Dolloff; Jessica Elaine Thaxton; Frank Marcoux	LEUKOGENE THERAPEUTICS, INC.
R41CA265655	An integrated strategy using a serum and imaging biomarker for the early detection of pancreatic cancer	Aatur Dilip Singhi; Pinku Mukherjee; Anirban Maitra; Ru Zhou; Ohad Ilovich	OncoTab (United States)
R42CA217482	Development of a protein drug for pancreatic cancer treatment	Zhi-Ren Liu	PRODA BIOTECH, LLC

Project Number	Title	Principal investigator(s)	Institution
R42CA239853	Preclinical Development of ACXT-3102 for the Treatment of Pancreatic Adenocarcinoma (PDAC)	Brian A Vantine; Michael S Kinch; Dirk M Spitzer; Diane Renee Mould; Bradley T Keller; Janice A. Lansita; John Springer; Robert H Mach; William G Hawkins; Andrea Wang-Gillam	ACCURONIX THERAPEUTICS, INC.
R43CA217400	First-in-class TREM-1 inhibitors in combination therapy for pancreatic cancer	Alexander B Sigalov	SignaBlok (United States)
R43CA221602	Development of a vault nanovaccine for pancreatic cancer immunotherapy	Gayle Boxx; Jan Mrazek; Don J Diamond; Edwin Manuel; Marcela D'Alincourt Salazar	AUKERA, INC.
R43CA232844	Development of Inhibitors of cANGPTL4 for Pancreatic Cancer Therapeutics	Sara J Cooper; Anuj Singhal; Omar Moukha-Chafiq; Corinne E Augelli-Szafran; Rebecca Boohaker; Narender Singh	CFD Research Corporation (United States)
R43CA246827	Translational Development of a Targeted and Stroma-breaking Nanoparticle Drug for Pancreatic Cancer Therapy	Bassel Fouad Ei-Rayes; Lei Zhu; Lily Yang	MIGRA-THERAPEUTICS, LLC
R43CA250780	OPN neutralization monoclonal antibody 100G2 for human pancreatic cancer immunotherapy	Roni J Bollag; Kebin Liu; Asha Nayak; Priscilla S Redd; Jin-Xiong She	CHEMEDIMMUNE, INC.
R43CA254493	Development of personalized ex vivo predictive technology for rapidly matching patient tumors with chemotherapy regimens before treatment	Lisa Walker Johnson; Karim I Budhwani; Christopher M Krebs	CERFLUX, INC.
R43CA254794	MyD88 fusion protein with antigen specific T Cell therapy for enhanced response in solid tumors	Beau Richard Webber; Samantha Dunmire; Andrew Fleszar; Ingunn Stromnes; David Andrew Largaespada; Branden S Moriarity	LUMINARY THERAPEUTICS, INC.

Project Number	Title	Principal investigator(s)	Institution
R43CA254820	Simultaneous Targeting of Tumor and Stroma Cells to Enhance Solid Tumor CAR-T Cell Therapy	Beau Richard Webber; Ingunn Stromnes; Samantha Dunmire; Branden S Moriarity; David Andrew Largaespada; Nicole Son; Aaron Lebeau	LUMINARY THERAPEUTICS, INC.
R44CA183265	FrostBite - A Unique Catheter for Endoscopic Cryoablation	John M Baust	Cell Preservation Services (United States)
R44CA199058	A Prognostic Blood Test to Monitor Pancreatic Cancer Treatment by MiRNA Profiling	Ravi F Saraf	VAJRA INSTRUMENTS, INC.
R44CA203090	Pancreatic Ductal Adenocarcinoma Targeted Ultrasound Contrast Agent Development	Sanjiv S Gambhir; Evan Charles Unger	NuvOx Pharma (United States)
R44CA203336	Immuno-Oncology for Pancreatic Cancer: A Combination Clinical Trial with Chemotherapy and Radiation	Estuardo Aguilar-Cordova; Laura K Aguilar	Advantagene (United States)
R44CA206663	Novel MAP Kinase Pathway Inhibitors to Treat Pancreatic Ductal AdenoCarcinoma	Peter Qinhua Huang; Ahmed Samatar	ZENO MANAGEMENT, INC
R44CA217400	First-in-class TREM-1 inhibitors in combination therapy for pancreatic cancer	Alexander B Sigalov	SignaBlok (United States)
R44CA221374	Generation of antibody-drug conjugates by proximity-based sortase-mediated ligation	Feifan Yu; Ian A Blair; Andrew Tsourkas; Joseph B Rucker	ALPHATHERA, INC.
R44CA224460	Implantable iontophoresis chemotherapy delivery device for direct infusion of gemcitabine into pancreatic adenocarcinoma: Device development and First-in-Human clinical trial	William Daunch	ADVANCED CHEMOTHERAPY TECHNOLOGIES, INC.
R44CA224472	Development of a DCLK1 siRNA Nanoparticle as Targeted Therapy to Treat Pancreatic Cancer	Eliseu O De Oliveira	COARE HOLDINGS, INC.

Project Number	Title	Principal investigator(s)	Institution
R44CA224994	Ultra-High Content Analysis (UHCA) of Single Cells in Tissue: 60+ channel immunofluorescence labeling kits and companion imaging software for everyone	Michel Nederlof	QUANTITATIVE IMAGING SYSTEMS, LLC
R44CA228695	Development of GPER Agonists as Cancer Therapeutics	Eric R Prossnitz; Todd W Ridky; Tina Garyantes; Christopher Natale	LINNAEUS THERAPEUTICS, LLC
R44CA233157	Selection and preclinical development of a bacteria-targeting, non-antibiotic lead candidate to improve cancer chemotherapy outcomes	Ward Peterson	SYMBERIX, INC.
R44CA235991	Targeting LIF/LIFR in pancreatic cancer	Sushil Kumar; Hareesh B Nair	Evestra (United States)
R44GM113351	High-specificity affinity reagents for the detection of glycan sialylation	Loretta Yang	Lectenz Bio (United States)
R50CA211425	Defining and targeting mechanisms of pancreas cancer pathogenesis	Martin Whittle	Fred Hutchinson Cancer Research Center
R50CA211437	Revealing cancer metabolism via mass spectrometry and isotope tracers	Wenyun Lu	Princeton University
R50CA211462	Critical resources provided by UNMC RAP biorepository stimulate cancer research	Paul M Grandgenett	University of Nebraska Medical Center
R50CA211506	Preclinical Models for Cancer Therapeutic Development	Youngkyu Park	Cold Spring Harbor Laboratory
R50CA232985	Targeting the Immunosuppressive Tumor Microenvironment in Pancreatic Cancer	Yaqing Zhang	University of Michigan Ann Arbor
R50CA233186	The role of DCLK1 in the initiation of pancreatic ductal adenocarcinoma and colorectal cancer	Dongfeng Qu	University of Oklahoma Health Sciences Center
R50CA251836	Mutant p53 gain-of-function as an actionable target in cancer therapy	Alice Nemajerova	Stony Brook University
R56DK123079	Unraveling the Role of NADPH Oxidase in Inflammation-associated Pancreatic Diseases	Weiqin Lu	Stony Brook University

Project Number	Title	Principal investigator(s)	Institution
SC1GM140907	Dissecting mechanisms of tumor initiation via immunomodulation	Geou-Yarh Liou	Clark Atlanta University
SC1GM140982	Targeting ribosome biogenesis and desmoplastic tumor microenvironment for the treatment of advanced pancreatic cancer	Manu M. Sebastian; Subhash Chauhan; Manish Tripathi; Bilal B Hafeez	The University of Texas Rio Grande Valley
SC3GM136647	Encapsulation and delayed release of gemcitabine by aluminum metal-organic frameworks	Alexandr Samokhvalov	Morgan State University
U01CA152653	Detection and prognosis of early-stage pancreatic cancer by interdependent plasma markers	Brian Haab; Peter Allen; Randall E Brand	Van Andel Institute
U01CA198846	UCLA Multifunctional Mesoporous Silica Nanoparticle Platform for Treatment of Pancreas Cancer	Andre E Nel; Timothy Donahue; Jeffrey Zink; Huan Meng	University of California, Los Angeles
U01CA198913	Stroma Breaking Theranostic Nanoparticle for Targeted Pancreatic Cancer Therapy	Hui Mao; Lily Yang	Emory University
U01CA199235	Identification of synthetic lethal interactors in pancreatic cancer	Adrienne Cox; Channing J. Der	University of North Carolina at Chapel Hill
U01CA202241	ECM geometrical and mechanical properties modulate RTK signaling	Valerie M Weaver; Jay T. Groves	University of California, Berkeley
U01CA210171	Circulating Biomarker Consortium for Pancreatic Cancer Early Detection	Brian M Wolpin	Dana-Farber Cancer Institute
U01CA210240	Pancreatic Cancer Detection Consortium	Michael A Hollingsworth	University of Nebraska Medical Center
U01CA213862	Nanovaccine platforms to combat pancreatic cancer	Aliasger Karimjee Salem; Maneesh Jain; Balaji Narasimhan	Iowa State University
U01CA214263	Circulating Biomarkers and Imaging for Early Detection of Pancreatic Cancer	Ann M Killary; Subrata Sen	The University of Texas MD Anderson Cancer Center
U01CA216449	Sensitization to Chemoradiation by Therapeutic Targeting of the DNA Damage Response	Theodore S Lawrence	University of Michigan Ann Arbor

Project Number	Title	Principal investigator(s)	Institution
U01CA216468	Enhancing Chemoradiation Efficacy through Unbiased Drug Discovery Approaches	Steven H Lin; Sunil Krishnan	The University of Texas MD Anderson Cancer Center
U01CA217665	Peptide-based targeted molecular imaging for early detection in pancreatic cancer	Julie L. Sutcliffe	University of California, Davis
U01CA217842	Integrative bioinformatics and functional characterization of oncogenic driver aberrations in cancer	Benjamin Deneen; Gordon B. Mills	Oregon Health & Science University
U01CA221046	Pretargeted Clinical Imaging of CA19.9 in Pancreatic Cancer	Brian M Zeglis; Jason S Lewis	Memorial Sloan Kettering Cancer Center
U01CA224012	Comparative analysis between patient-derived models of pancreatic ductal adenocarcinomas and matched tumor specimens	Emek Demir; Lisa M Coussens; Jonathan Brody; Rosalie Sears	Oregon Health & Science University
U01CA224145	Interrupting Cellular Crosstalk in the Immunosuppressive Microenvironment of Pancreas Cancer	Howard Crawford; Marina Pasca Di Magliano	University of Michigan Ann Arbor
U01CA224146	Systematic interrogation of the pancreatic cancer microenvironment in patient-derived specimens	William C Hahn	Dana-Farber Cancer Institute
U01CA224175	Defining neoantigen immunodominance for antigen selection and biomarker discovery in human pancreatic cancer immunotherapy	Steven D Leach; Vinod Balachandran	Memorial Sloan Kettering Cancer Center
U01CA224193	Disrupting the immune and drug-privileged microenvironment in pancreas cancer	Sunil Hingorani	Fred Hutchinson Cancer Research Center
U01CA224348	Reprogramming PDAC tumor microenvironment to improve immunotherapy	Rakesh K Jain; Yves Boucher	Massachusetts General Hospital
U01CA226158	Subpopulations of Pancreatic Cancer Cells Defined by Glycan Markers	Brian Haab; Randall E Brand	Van Andel Institute
U01CA233581	Sialylation-dependent mechanisms driving pancreatic cancer progression	Lance Wells; Susan L Bellis	University of Alabama at Birmingham

Project Number	Title	Principal investigator(s)	Institution
U01CA242936	Computational pathology software for integrative cancer research with three-dimensional digital slides	Jun Kong; Bassel El-Rayes; Gregory Lesinski; Fusheng Wang	Georgia State University
U01CA243007	Optimal control models of epithelial-mesenchymal transition for the design of pancreas cancer combination therapy	Ben Stanger; Babatunde A Ogunnaike; Todd W Bauer; Matthew J Lazzara	University of Virginia
U01CA247283	Multi-Ancestry Mapping of Pancreatic Cancer Susceptibility Loci	Alison P Klein	Johns Hopkins University
U01CA250186	The Oral Mycobiome and Risk of Pancreatic Cancer	George Miller; Jiyoung Ahn; Huilin Li; Diane Simeone; Richard B Hayes; Neal Freedman; Eric Jacobs; Cristina H Hajdu	New York University
U01CA250549	Development and implementation of multiplex methods to understand the biology and heterogeneity of patient-derived cancer models	William C Hahn	Dana-Farber Cancer Institute
U01CA252965	Digital Nanoplasmonic Quantification of Tumor-derived Extracellular Vesicles in Plasma Microsamples	Subrata Sen; Hua Lu; Tony Y. Hu	Tulane University
U01CA265697	Synthetic circuits that drive infiltration of therapeutic T cells into immunologically cold tumors	Hana El-Samad; Margaret A Tempero; Christopher Garcia; Jason Cyster; Wendell A Lim; Antonio Ribas; Eric Collisson	University of California, San Francisco
U01DK108288	The Exocrine and Endocrine Pancreas in Type 2 Diabetes, Pancreatitis and Cancer	Gloria M Petersen; Santhi Swaroop Vege	Mayo Clinic
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	Marina Basina; Aida Habtezion; Walter Gwang-Up Park; Shreyas Vasanawala; Seung K Kim; Zachary Sellers; Bryant Lin	Stanford University

Project Number	Title	Principal investigator(s)	Institution
U01DK108306	Consortium for the study of chronic pancreatitis, diabetes and pancreatic cancer / Pittsburgh Clinical Center	Dhiraj Yadav; David Whitcomb	University of Pittsburgh
U01DK108314	Greater Los Angeles Clinical Center of the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer	Mark Goodarzi; Stephen Pandol	Cedars-Sinai Medical Center
U01DK108320	Administrative Supplement (NoD)	Kenneth Cusi; Christopher E Forsmark; Steven J Hughes	University of Florida
U01DK108323	Indiana University (IU) Clinical Center for Chronic Pancreatitis Clinical Research Network	Evan Fogel	Indiana University Purdue University Indianapolis
U01DK108326	ALTERED MICROBIOME IN PANCREATITIS, DIABETES AND PANCREATIC CANCER	William E Fisher	Baylor College of Medicine
U01DK108327	The Ohio State University Chronic Pancreatitis Diabetes Pancreas Cancer (CPDPC) Clinical Center	Darwin Lewis Conwell; Philip A. Hart	The Ohio State University
U01DK108328	Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer: Coordinating and Data Management Center (CSCPDPC-CDMC)	Anirban Maitra; Ying Yuan; Liang Li	The University of Texas MD Anderson Cancer Center
U01DK108332	Chronic Pancreatitis, Diabetes and Pancreatic Cancer: A Prospective Approach	Stephen K Van Den Eeden	Kaiser Permanente
U01DK126300	University of Minnesota Clinical Center for the Study of Pancreatic Disease	Matthew Aaron Armfield; Gregory J Beilman; Guru V Trikudanathan; Benjamin D Spilseth; Melena D Bellin; Martin Freeman; Sarah Jane Schwarzenberg; Emil Lou; Srinath Chinnakolta	University of Minnesota

Project Number	Title	Principal investigator(s)	Institution
U01DK126365	The Texas-Louisiana Alliance to Study Chronic Pancreatitis, Diabetes and Pancreatic Cancer	Nirav Thosani; Andrew D Rhim; Elmer V. Bernstam; Anirban Maitra; Florencia Mcallister; John T Cole; Wenjin Jim Zheng; Suresh T. Chari; Eugene J Koay; Sushovan Guha	The University of Texas MD Anderson Cancer Center
U01HL143365	Biomarkers and mechanisms in cancer associated thrombosis	Elliot Chaikof; Jeffrey Zwicker; Robert Flaumenhaft	Beth Israel Deaconess Medical Center
U01HL143402	Novel approaches to improve prediction of cancer-associated thrombosis	Alok A Khorana; Keith Mccrae	Cleveland Clinic Lerner College of Medicine
U01HL143403	Targeting the Plasminogen Activation System to Limit Pancreatic Cancer Progression and Associated Thrombosis	Alisa S. Wolberg; Melissa L. Fishel; Matthew Flick; Bumsoo Han	University of North Carolina at Chapel Hill
U24CA209996	Building protected data sharing networks to advance cancer risk assessment and treatment	Ian Foster	University of Chicago
U24CA210986	Center of Excellence for High Throughput Proteogenomic Characterization	Michael A Gillette; Steven A Carr	Broad Institute
U24CA224020	Pancreatic Ductal Adenocarcinoma Translational Resource Center (PATReC)	Anirban Maitra; Subrata Sen	The University of Texas MD Anderson Cancer Center
U24CA231858	Penn Quantitative MRI Resource for Pancreatic Cancer	Peter J Odwyer; Rong Zhou; Mark Rosen	University of Pennsylvania
U2CCA233284	Transition to Metastatic State: Lung Cancer, Pancreatic Cancer and Brain Metastasis	Christine Anne Iacobuzio-Donahue; Dana Pe'Er	Memorial Sloan Kettering Cancer Center
U2CCA233303	Washington University Human Tumor Atlas Research Center	Li Ding; Samuel Achilefu; Ryan C. Fields; William E. Gillanders	Washington University in St. Louis
U54CA156734	1/2 The University of Massachusetts, Boston - Dana-Farber/Harvard Cancer Center U54 Comprehensive Partnership for Cancer Disparities Research	Adan Colon-Carmona; Jill A Macoska; Kasisomayajulia Viswanath	University of Massachusetts Boston
U54CA209997	Structural and Functional Biology-based analysis of non-oncogene cancer dependencies	Andrea Califano; Itshack Pe'Er; Barry Honig; Peter A Sims; Diana Murray	New York Presbyterian Hospital
U54CA210181	Center for Immunotherapeutic Transport Oncophysics	Haifa Shen; Jenny C Chang	Houston Methodist

Project Number	Title	Principal investigator(s)	Institution
U54CA210190	Center for Modeling Tumor Cell Migration Mechanics	David J Odde	University of Minnesota
U54CA217377	Quantitative and functional characterization of therapeutic resistance in cancer	Scott R. Manalis; Douglas A. Lauffenburger	Massachusetts Institute of Technology
U54CA224065	University of Texas PDX Development and Trial Center	Jack Roth; Funda Meric-Bernstam	The University of Texas MD Anderson Cancer Center
U54CA224083	Washington University PDX Development and Trial Center	Ramaswamy Govindan; Li Ding; Shunqiang Li	Washington University in St. Louis
U54CA233396	1/3 Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center	Romonia Renee Reams	Florida Agricultural and Mechanical University
U54CA233444	Investigations of Black Ancestry on Pancreatic Cancer Tumor Biology for US-related Cancer Health Disparities	Jose G Trevino; Yingwei Yao; Srikar Chamala; Andrea Riner; Folakemi T Odedina	University of Florida
U54CA233465	3/3 Florida-California Cancer Research, Education and Engagement (CaRE2) Health Equity Center	John D. Carpten	University of Southern California
UG3CA232820	Disposable Perfusion Phantom for Accurate DCE-MRI Measurement of Pancreatic Cancer Therapy Response	Harrison Kim	University of Alabama at Birmingham
UH2CA238926	HRD-IA signatures in pancreatic ductal adenocarcinoma	Michael T Barrett; Dora M Lam-Himlin; Todd Alan Dewees; Tanios Sam Bekaii-Saab	Mayo Clinic
UH2CA263954	Imaging the native 3D architecture of pancreatic and breast tumor patient tissue at single-cell resolution	Tao Ju; Ryan C Fields; James A. Fitzpatrick; William E Gillanders; Stephen T Oh; Li Ding	Washington University in St. Louis
UH3CA232820	Disposable Perfusion Phantom for Accurate DCE-MRI Measurement of Pancreatic Cancer Therapy Response	Harrison Hyunki Kim	University of Alabama at Birmingham
UM1CA182934	The NYU Women's Health Study	Anne Zeleniuch-Jaquotte	New York University
UM1HG009426	Center for Functional Validation and Evaluation of ENCODE Enhancer Regions	Barbara E Stranger; Kevin P White	University of Chicago; Tempus Labs (United States)

Project Number	Title	Principal investigator(s)	Institution
ZIAAI000614	NOX family NADPH oxidases: roles in innate immunity and inflammatory disease	Thomas Leto	National Institute of Allergy and Infectious Diseases
ZIABC010020	Clinical Trials with Immunotoxins	Ira Pastan	Division of Basic Sciences - NCI
ZIABC010298	Growth Regulation Section	Ira Pastan	Division of Basic Sciences - NCI
ZIABC010391	Role of Trk Receptors in the Development and Function of Non-neuronal Structures	Lino Tessarollo	Division of Basic Sciences - NCI
ZIABC010425	Strategies for Cancer Immunotherapy Clinical Trials	Jeffrey Schlom	Division of Basic Sciences - NCI
ZIABC010476	Time Domian Electron Paramagnetic Resonance Imaging	Murali Cherukuri Krishna	Division of Basic Sciences - NCI
ZIABC010477	Overhauser Enhanced Magnetic Resonance Imaging (OMRI)	Murali Cherukuri Krishna	Division of Basic Sciences - NCI
ZIABC011162	Integrative Molecular Profiling of Human Pancreatic Cancer	Syed Perwez Hussain	Division of Basic Sciences - NCI
ZIABC011185	Role of Immune and Inflammation Mediators in Progression of Pancreatic Cancer	Syed Perwez Hussain	Division of Basic Sciences - NCI
ZIABC011267	Preclinical drug development in pancreatic cancer	Udo Rudloff	Division of Basic Sciences - NCI
ZIABC011343	Clinical protocols for the treatment of gastrointestinal cancer	Tim Greten	Division of Basic Sciences - NCI
ZIABC011547	Cancer Immunotherapy Clinical Trials	Julius Strauss	Division of Basic Sciences - NCI
ZIABC011652	Mesothelin-targeted immunotoxins in Pancreatic Cancer	Christine Alewine	Division of Basic Sciences - NCI
ZIABC011739	Development and Preclinical Applications of Pancreatic Adenocarcinoma Models	Shyam K Sharan	Division of Basic Sciences - NCI
ZIABC011798	Identification of genomic regulatory elements in pancreas cells	Hatice Arda	Division of Basic Sciences - NCI
ZIABC011865	Breast and Other Carcinoma Clinical Trials Using Immunotherapies	Margaret E Gatti-Mays	Division of Basic Sciences - NCI

Project Number	Title	Principal investigator(s)	Institution
ZIABC011886	First in Human Trials of ProAgio, a Cytotoxin	Christine Alewine	Division of Basic Sciences - NCI
ZIABC012041	Rare Exocrine Tumors of the Pancreas	Christine Alewine	Division of Basic Sciences - NCI
ZIACP010120	Studies of Occupational Cancer	Qing Lan	Division of Cancer Epidemiology and Genetics
ZIACP010136	Cancer Risk in Human Populations	Debra Silverman	Division of Cancer Epidemiology and Genetics
ZIACP010193	Whole Genome Scan in the Pancreatic Cancer Cohort Consortium (PanScan)	Rachael Solomon	Division of Cancer Epidemiology and Genetics
ZIACP010195	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Demetrius Albanes	Division of Cancer Epidemiology and Genetics
ZIACP010202	Biochemical, molecular, and dietary studies for pancreatic cancer within PLCO	Rachael Solomon	Division of Cancer Epidemiology and Genetics
ZIADK053101	Cellular Basis Of Action Of Gastrointestinal Peptides/Growth factors	Robert Jensen	National Institute of Diabetes and Digestive and Kidney Diseases
ZIAEB000094	Mechanobiology	Alexander X. Cartagena-Rivera	National Institute of Biomedical Imaging and Bioengineering
ZIATR000019	Studies of Tumor-Penetrating Microparticles for Pancreatic Cancer	Donald Lo	National Center for Advancing Translational Sciences
ZIATR000178	Development of small molecule agonists of the parathyroid hormone receptor type-1 (PTHR1) as potential new therapeutics for the treatment of osteoporosis	Noel Southall	National Center for Advancing Translational Sciences
ZIATR000262	Advanced development of human mutant IDH1 inhibitors (Chemical Biology Consortium/NCI Experimental Therapeutics Collaboration)	Matthew Hall	National Center for Advancing Translational Sciences

Project Number	Title	Principal investigator(s)	Institution
ZIATR000278	Metarrestin for the Treatment of Pancreatic Cancer	Donald Lo	National Center for Advancing Translational Sciences
ZIATR000358	Development of small molecule inhibitors of ULK1	Matthew Hall	National Center for Advancing Translational Sciences
ZIDBC011540	Thoracic and Gastrointestinal Malignancies Branch Clinical Core	Raffit Hassan	Division of Basic Sciences - NCI
ZIEBC011653	Clinical Support	Christine Alewine	Division of Basic Sciences - NCI
ZIABC011861	Evaluating outcomes for patients with primary-metastatic gastrointestinal cancer	Jonathan Hernandez	Division of Basic Sciences - NCI
ZIABC011732	Discovery of combination therapy for KRAS mutant cancer	Ji Luo	Division of Basic Sciences - NCI
ZIACP010197	Physical Activity, Energy Balance, and Cancer	Demetrius Albanes; Rachael Stolzenberg-Solomon	Division of Cancer Epidemiology and Genetics
ZIABC010440	Protein Structure, Stability, and Amyloid Formation	Ruth Nussinov	Division of Basic Sciences - NCI
ZIABC011964	Transcriptomic origins of cancer	Sridhar Hannenhalli	Division of Basic Sciences - NCI

FY 2019, 2020, and 2021 NIH Projects Related to SCLC

Table 11: FY 2019, 2020, and 2021 NIH Projects Related to SCLC

Project Number	Title	Principal investigator(s)	Institution
F30CA228314	Phosphorylation of ASCL1 to disrupt oncogenic activity in SCLC	Demetra P Kelenis	The University of Texas Southwestern Medical Center
F30CA232475	Role of MYC Family Members in Driving Chemoresistance in Small Cell Lung Cancer	Eli Grunblatt	University of Washington
F30CA247078	Systems-level mechanisms of small cell lung cancer dynamics	Samantha Beik	Vanderbilt University
F31CA225119	Elucidating and Targeting EZH2 in the DNA Damage Response in Small Cell Lung Cancer	Allyson Koyen	Emory University

Project Number	Title	Principal investigator(s)	Institution
F31CA239424	Credentialing Delta-like 3 (DLL3) as an oncoprotein and immunotherapeutic target in neuroblastoma	Nathan M Kendsersky	University of Pennsylvania
F31CA243149	Tracing Intratumoral Cellular Heterogeneity using genetic barcoding in small cell lung cancer	Michael S Kareta; Jill M Weimer; Hannah G Wollenzien	University of South Dakota
F31CA254244	Characterizing ALCAM as an oncoprotein and immunotherapeutic target in neuroblastoma	Jarrett Lindsay	University of Pennsylvania
F31CA254405	Elucidating the molecular determinants of p53-mediated pleiotropic effects	Jonuelle Acosta	University of Pennsylvania
F31CA257169	Molecular mechanisms of NFIB in small cell lung cancer metastasis	Julie H Ko; Julien Sage	Stanford University
F31CA265131	Determining the role of ASCL1 in neuroendocrine prostate cancer	Ping Mu; Kathia E Rodarte; Jane E Johnson	The University of Texas Southwestern Medical Center
F99CA234942	Understanding metabolic vulnerabilities in cancer and the impact the tumor microenvironment has on cancer progression	Shonagh Russell	University of South Florida
F99CA245471	Mechanisms of Cell Cycle and Cell Identity Regulation that Influence Sensitivity to Targeted Therapies	Andrea C Chaikovsky	Stanford University
K00CA223015	Identifying Genetic Drivers of the Immunosuppressive Tumor Microenvironment in Lung Cancer	Gurkan Mollaoglu	Icahn School of Medicine at Mount Sinai
K00CA234942	Understanding metabolic vulnerabilities in cancer and the impact the tumor microenvironment has on cancer progression	Shonagh Russell	Duke University
K08CA222657	New Therapeutic Targets in Small Cell Lung Cancer that are Epistatic or Synthetic Lethal with pRB Loss	Matthew G Oser	Dana-Farber Cancer Institute

Project Number	Title	Principal investigator(s)	Institution
K08CA237832	Dissecting and overcoming cross-resistance to DNA damaging agents in SCLC	Benjamin Drapkin	The University of Texas Southwestern Medical Center
K08CA241309	Genomic characterization of tumor heterogeneity in recurrent small cell lung cancer through research autopsy	Hui-Zi Chen	Medical College of Wisconsin; The Ohio State University
K08HL129081	Genetic and Molecular Dissection of Pulmonary Neuroendocrine (NE) Cell Development	Christin S Kuo	Stanford University
K99CA226353	Investigation of sub-lineages in pulmonary neuroendocrine cells and identification of the cells of origin of small cell lung cancer	Harold E. Varmus; Shuibing Chen; Olivier Elemento; Charles M Rudin; Huanhuan Chen; Benjamin David Cosgrove; Hans-Willem E Snoeck	Cornell University
K99CA252001	Microenvironment-driven electrical regulation of primary and secondary brain tumor progression	Humsa Venkatesh; Robert C Malenka; Michelle Monje; Julien Sage	Stanford University
P01CA250984	Identifying Metabolic Vulnerabilities in Lung Cancer	Eric B. Haura; Elsa R Flores	Moffitt Cancer Center
P30CA016672	MD Anderson Cancer Center Support Grant	Peter W. Pisters	The University of Texas MD Anderson Cancer Center
P30CA043703	Case Comprehensive Cancer Center Support Grant	Stanton L. Gerson	Case Western Reserve University
P30CA142543	UT Southwestern Medical Center Simmons Comprehensive Cancer Center	Carlos L. Arteaga	The University of Texas Southwestern Medical Center
P50CA070907	Targeting Lung Cancer Vulnerabilities	Jack Roth; John V Heymach; John D Minna	The University of Texas Southwestern Medical Center
P50CA228944	Fred Hutchinson Cancer Research Center Lung SPORE	A M Houghton	Fred Hutchinson Cancer Research Center
R00CA226353	Investigation of sub-lineages in pulmonary neuroendocrine cells and identification of the cells of origin of small cell lung cancer	Huanhuan Chen	University of Chicago

Project Number	Title	Principal investigator(s)	Institution
R01CA181449	Interrogation of MLL2 as a tumor suppressor gene in lung cancer	David Macpherson	Fred Hutchinson Cancer Research Center
R01CA197936	Determinants of acquired resistance in small cell lung cancer	Charles M Rudin	Memorial Sloan Kettering Cancer Center
R01CA200547	Investigating CREBBP as a tumor suppressor in small cell lung cancer	David Macpherson	Fred Hutchinson Cancer Research Center
R01CA200905	Modulation of BAK in Lung Cancer Therapeutics	Xingming Deng	Emory University
R01CA201513	Notch signaling in small cell lung carcinoma	Julien Sage	Stanford University
R01CA202956	Optimizing Treatment of Lung Cancer Patients with Comorbidities	Juan P Wisnivesky; Chung Kong	Icahn School of Medicine at Mount Sinai
R01CA206540	Molecular and cellular mechanisms of SCLC metastasis	Julien Sage	Stanford University
R01CA207295	Therapeutic strategies for targeting PARP1 in small cell lung cancer	Lauren A Byers	The University of Texas MD Anderson Cancer Center
R01CA211095	Role of KDM5A in pRB-mediated differentiation	Elizaveta V. Benevolenskaya	University of Illinois at Chicago
R01CA213448	Immuno-PET imaging of high-grade neuroendocrine lung tumors using 89Zr-rovalpituzumab, a DLL3-targeting monoclonal antibody	Jason S Lewis; Charles M Rudin; John T Poirier	Memorial Sloan Kettering Cancer Center; New York University
R01CA218545	Novel approach to attenuate small cell lung cancer growth and metastasis	Mohd Wasim Nasser	University of Nebraska Medical Center
R01CA230032	Vulnerability of SCLC based on bi-allelic genetic inactivation of RB1 and TP53	Edward L Schwartz; Hongling Zhao	Albert Einstein College of Medicine
R01CA243328	Tumor-specific autoantibodies for SCLC early detection	A M Houghton; Paul D. Lampe	Fred Hutchinson Cancer Research Center
R01CA248762	Investigating Max as a tumor suppressor gene in small cell lung cancer and other neuroendocrine tumors	David Macpherson; Robert Neil Eisenman	Fred Hutchinson Cancer Research Center

Project Number	Title	Principal investigator(s)	Institution
R01CA251147	Mechanisms of Arginine Deprivation in Small Cell Lung Cancer	Benjamin L Witt; Xiaoyang Zhang; Elizabeth A Leibold; David H Lum; Ralph J Deberardinis; Benjamin T Spike; Brian K. Dalley; Martin Mcmahon; Kenneth M Boucher; John Stephen Bomalaski; Trudy G Oliver	University of Utah
R01CA251753	The Translational Regulation of Pro-apoptotic Genes	Wayne Miles	The Ohio State University
R01CA258784	Targeting replication stress signaling to overcome immune evasion in small cell lung cancer	Glenn Heller; Charles M Rudin; Triparna Sen; Dana Pe'Er; Jedd D Wolchok; Matthew G Oser; Natasha Rekhtman; Taha Merghoub	Memorial Sloan Kettering Cancer Center
R01LM013352	Statistical Methods and Validation Analyses for the Integration of External Data in Clinical Trials	Rifaquat M Rahman; Steffen Ventz; Lorenzo Trippa; Susana Halabi	Dana-Farber Cancer Institute
R15CA161491	Capsaicin and small cell lung cancer therapy	Piyali Dasgupta; Monica A Valentovic	Marshall University
R21CA216066	Extracellular matrix regulation of lung adenocarcinoma signaling and drug responsiveness	Gregory H Underhill	University of Illinois at Urbana Champaign
R21CA216504	Identifying Therapeutic Vulnerabilities of c-MYC-driven Small Cell Lung Cancer	Trudy G Oliver	University of Utah
R21CA226322	Identification and Targeting of Chemotherapy Refractory Small Cell Lung Cancer	Afshin Dowlati	Case Western Reserve University
R21CA252387	PD-L1 inhibition promotes type I interferon responses, enhancing chemotherapy-induced cytotoxicity in cancer cells	George Stark; Hyeonjoo Cheon; Daniel J Lindner	Cleveland Clinic Lerner College of Medicine
R21CA256638	Novel Mechanisms Controlling SCLC Tumor Initiation	Robert E Lewis; Trudy G Oliver; Michael S Kareta; Ralph J Deberardinis	University of Nebraska Medical Center

Project Number	Title	Principal investigator(s)	Institution
R21HD104361	Regulating transcription of the key pulmonary neuroendocrine lineage driver ASCL1	Jane D. Johnson	The University of Texas Southwestern Medical Center
R35CA231997	Investigating molecular and cellular mechanisms of SCLC development to identify novel therapeutic strategies	Julien Sage	Stanford University
R35CA263816	Novel therapeutic development for small cell lung cancer	Jason S Lewis; Charles Sawyers; Glenn Heller; Dana Pe'Er; Charles M Rudin	Memorial Sloan Kettering Cancer Center
R37CA249305	The functional role of MAST1 in mediating a-synucleinopathies and related dementia	Lingtao Jin; Xiaobo Mao; Ted M Dawson	University of Florida
R43CA236023	JAA-F11 Anti-Thomsen-Friedenreich Antigen Targeted Imaging for Lung Cancer Differential Diagnosis	James Olson; Grace Dy; Bradley Turner; Pamela A Hershberger; Kate Rittenhouse-Olson; Dominick Lamonica; Bruce A Davidson; Munawwar Sajjad	For Robin (United States)
R43CA236260	Novel strategy to generate glycan-specific antibodies for cancer immunotherapy	Nai-Kong V Cheung; Joshua D Wilson; Matthew P Delisa; Brian Green; Sachdev Sidhu	Glycobia (United States)
R50CA243698	Modeling tumor heterogeneity and treatment resistance in small cell lung cancer	C Allison Stewart; Lauren A Byers	The University of Texas MD Anderson Cancer Center
R56ES014737	Modification of DNA Polymerase d by a Novel Mechanism During Replication Stress	Marietta Y Lee; Zhongtao Zhang	New York Medical College
U01CA209414	The Boston Lung Cancer Survival Cohort	David Christiani	Harvard University
U01CA213273	Novel therapeutic approaches for enhancing anti-tumor immunity in SCLC	John V Heymach; Lauren A Byers; Julien Sage	The University of Texas MD Anderson Cancer Center
U01CA213285	Development of Risk and Early Detection Biomarker for Small Cell Lung Cancer	Samir M. Hanash	The University of Texas MD Anderson Cancer Center
U01CA213330	Extracellular Vesicles in Small Cell Lung Cancer Early Detection	Ly J Lee; Serge Nana-Sinkam	Virginia Commonwealth University

Project Number	Title	Principal investigator(s)	Institution
U01CA213333	Targeting the transcriptional and epigenetic landscape in chemo-refractory Small-Cell Lung Cancer	Kwok Kin Wong; Nathanael Schiander Gray	New York University
U01CA213338	Developing ASCL1 and NeuroD1 lineage oncogene targeted therapy for small cell lung cancer	John D Minna	The University of Texas Southwestern Medical Center
U01CA213359	Clinical development of a DLL3-targeted theranostic for small cell lung cancer	Jason S Lewis; Charles M Rudin; John T Poirier	Memorial Sloan Kettering Cancer Center; New York University
U01CA215845	Phenotype Transitions in Small Cell Lung Cancer	Carlos F. Lopez; Vito Quaranta	Vanderbilt University
U01CA220323	Using patient-derived models to understand drug responses in SCLC	Nicholas J Dyson	Massachusetts General Hospital
U01CA224276	Phenotype Interactions in SCLC Development and Detection	Alissa Weaver	Vanderbilt University
U01CA224293	Targeting BCAT1 and branched-chain amino acid metabolism for the detection and prevention of SCLC	Kwon-Sik Park	University of Virginia
U01CA224326	Studies of the initiation and progression of small cell lung cancer using cells derived by differentiation from human pluripotent stem cells	Harold E. Varmus	Cornell University
U01CA231776	Bioinformatic-Chemical Approach to Credential Molecular Targets to Combat Rapid Chemo-Radiation Resistance in SCLC	Christine Hann; Luigi Marchionni; Phuoc T Tran	Johns Hopkins University
U01CA231844	Genomic and Functional Identification of Chemotherapy Resistance Mechanisms in Small Cell Lung Cancer	Obi Lee Griffith; Ramaswamy Govindan; Trudy G Oliver	Washington University in St. Louis
U01CA231851	Molecular mechanisms of SCLC initiation and detection in mice and humans	Mark A Krasnow	Stanford University
U01CA233074	Targeting alternative splicing for TCR discovery in small cell carcinomas	Gay M Crooks; Owen N Witte; Yi Xing	University of California, Los Angeles

Project Number	Title	Principal investigator(s)	Institution
U01CA235625	Employing CRISPR inactivation screening and in vivo models towards improving treatments for SCLC	David Macpherson	Fred Hutchinson Cancer Research Center
U01CA242919	Exploiting POU2F3 addiction in the tuft cell variant of small cell lung cancer	Christopher Vakoc	Cold Spring Harbor Laboratory
U01CA253383	Understanding the molecular mechanism of a protein-recycling complex in small cell lung cancer treatment resistance.	Benjamin Lok; Brian Raught	University Health Network
U01CA256780	Molecular and immunological heterogeneity of Small Cell Lung Cancer (SCLC) and its impact on relapse and therapeutic response	Jianjun Zhang; Junya Fujimoto; Jing Wang; Carl Michael Gay; Lauren A Byers; John V Heymach; Marcelo Vailati Negrao	The University of Texas MD Anderson Cancer Center
U01CA256801	Optimizing Dual-Targeted and Dual-Armored CAR T Cells for Small Cell Lung Cancer	Renier J Brentjens; Christopher Hackett; Charles M Rudin; Sean Devlin	Memorial Sloan Kettering Cancer Center
U24CA213274	Coordinating center for the NCI small cell lung cancer research consortium	Charles M Rudin	Memorial Sloan Kettering Cancer Center
U54CA217450	Phenotype Heterogeneity and Dynamics in SCLC	Vito Quaranta	Vanderbilt University
U54MD007582	FAMU Center for Health Disparities Research	Karam F.A. Soliman	Florida Agricultural and Mechanical University
ZIABC006150	DNA Repair, Cell Cycle Checkpoints and Apoptosis as Targets for Anticancer Drugs	Yves Pommier	Division of Basic Sciences - NCI
ZIABC010449	Role of Novel Cytokine Secretoglobin (SCGB) 3A2 in Lung	Shioko Kimura	Division of Basic Sciences - NCI
ZIABC011115	Epigenetic Mechanisms of Gene Expression in Thoracic Malignancies	David Schrump	Division of Basic Sciences - NCI
ZIABC011418	Modulating Cancer Stem Cell Signaling in Thoracic Malignancies	David Schrump	Division of Basic Sciences - NCI
ZIABC011495	Integrative Molecular Epidemiology of Human Cancer	Curtis Harris	Division of Basic Sciences - NCI

Project Number	Title	Principal investigator(s)	Institution
ZIABC011672	Clinical Protocols in the Cancer Signaling Networks Section	Udayan Guha	Division of Basic Sciences - NCI
ZIABC011736	Preclinical Development of Therapeutics in Murine Models of Lung Cancer	Shyam K Sharan	Division of Basic Sciences - NCI
ZIABC011746	Development Therapeutics Branch Clinical Trials	Yves Pommier	Division of Basic Sciences - NCI
ZIABC011787	Predictive biomarker of BET bromodomain inhibitor in Small cell lung cancer	Haobin Chen	Division of Basic Sciences - NCI
ZIABC011793	Exploiting DNA Replicative Stress for Novel Small Cell Lung Cancer Therapies	Anish Thomas	Division of Basic Sciences - NCI
ZIABC011839	Developing an Effective BET bromodomain inhibitor Drug Combo to Target SCLC	Haobin Chen	Division of Basic Sciences - NCI
ZICBC011475	Genomics and Bioinformatics Group web site development and maintenance	William Reinhold	Division of Basic Sciences - NCI
ZICBC011497	RNA data development of cancer cell lines and patients.	William Reinhold	Division of Basic Sciences - NCI
ZICBC011622	Development of novel molecular or phenotypic databases	William Reinhold	Division of Basic Sciences - NCI
ZICBC011820	DNA methylation data development and for small cell lung cancer	William Reinhold	Division of Basic Sciences - NCI
ZICSC006537	Using Clinical Pharmacology Principles to Develop New Anticancer Therapies	William D. Figg	Division of Clinical Sciences - NCI
ZICSC006743	Signal Transduction Events and the Regulation of Cell Growth	Jane B Trepel	Division of Clinical Sciences - NCI

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.

Table 12: Funding for Chronic Diseases and Organ Systems

Research Area (Dollars in Millions)*	FY 2019	FY 2020	FY 2021
Auditory			
Otitis Media	$13	$10	$8
Brain Disorders	$6,954	$7,565	$7,963
ALS	$105	$107	$120
AD	$2,240	$2,683	$3,059
Aphasia	$43	$48	$51
Autism	$290	$294	$288
Baten Disease	$6	$10	$14
Brain Cancer	$359	$384	$415
Cerebral Palsy	$28	$35	$30
Epilepsy	$188	$198	$218
Frontotemporal Dementia	$158	$166	$164
Pick's Disease	$11	$11	$11
Huntington's Disease	$48	$49	$46
Traumatic Brain Injury[2209]	$134	$179	$185
Intellectual and Developmental Disabilities	$564	$595	$588
Autism	$290	$294	$288
Down Syndrome	$86	$111	$109
Fragile X Syndrome	$37	$41	$37
FASD[2210]	$34	$36	$38
Multiple Sclerosis	$111	$124	$126
Parkinson's Disease	$224	$242	$254
Ret Syndrome	$15	$15	$18

[2209] Name revised in FY 2021 from "Injury - Traumatic Brain Injury".

* The NIH does not expressly budget by category. The annual estimates reflect amounts that change as a result of science, actual research projects funded, and the NIH budget. The research categories are not mutually exclusive. Individual research projects can be included in multiple categories so amounts depicted within each column of this table do not add up to 100 percent of NIH-funded research.

[2210] Name revised in FY 2021 from "Fetal Alcohol Syndrome".

+ Indicates a new category. Funding support data not available prior to the initial year reported

Research Area (Dollars in Millions)*	FY 2019	FY 2020	FY 2021
Schizophrenia	$263	$256	$242
Tourette Syndrome	$11	$10	$10
Tuberous Sclerosis	$25	$27	$26
Cancer	$6,520	$7,035	$7,362
Brain Cancer	$359	$384	$415
Breast Cancer	$709	$788	$731
Cervical Cancer	$106	$113	$120
Childhood Leukemia	$178	$181	$240
Colo-Rectal Cancer	$294	$319	$335
Esophageal Cancer	+	$37	$45
HPV and/or Cervical Cancer Vaccine	$40	$47	$46
Liver Cancer	$127	$130	$128
Lung Cancer	$419	$447	$451
Lymphoma	$248	$265	$281
Hodgkin's Disease	$12	$18	$21
Neuroblastoma	$58	$66	$109
Ovarian Cancer	$168	$188	$178
Pancreatic Cancer	$219	$230	$242
Prostate Cancer	$263	$264	$284
Stomach Cancer	+	$24	$38
Uterine Cancer	$36	$32	$29
Cardiovascular	$2,394	$2,536	$2,544
Atherosclerosis	$400	$387	$413
Heart Disease	$1,443	$1,606	$1,536
Heart Disease – Coronary Heart Disease	$421	$408	$380
Hypertension	$266	$301	$292
Chronic Fatigue Syndrome	$15	$15	$17
Dental/Oral and Craniofacial Disease	$613	$628	$638
Temporomandibular Muscle/Joint Disorder	$17	$17	$14
Diabetes	$1,099	$1,156	$1,124
Digestive Diseases	$2,173	$2,273	$2,404
Digestive Diseases – (Gallbladder)	$16	$13	$20
Digestive Diseases – (Peptic Ulcer)	$8	$8	$9
Inflammatory Bowel Disease	$163	$177	$182
Crohn's Disease	$76	$86	$88
Liver Disease	$851	$845	$887
Chronic Liver Disease and Cirrhosis	$351	$368	$374

Research Area (Dollars in Millions)*	FY 2019	FY 2020	FY 2021
Hepatitis	$378	$362	$373
Hepatitis A	$3	$5	$7
Hepatitis B	$67	$70	$149
Hepatitis C	$150	$120	$115
Endocrine			
Estrogen	$243	$259	$274
Diethylstilbestrol (DES)	$2	$1	$3
Eye Disease and Disorders of Vision	$985	$1,012	$1,070
Macular Degeneration	$124	$107	$102
Hematology	$1,474	$1,642	$1,641
Cooley's Anemia	$22	$21	$19
Sepsis[2211]	$137	$155	$167
Sickle Cell Disease	$139	$145	$146
Immune			
Allergic Rhinitis (Hay Fever)	$7	$7	$7
Asthma	$313	$338	$310
Autoimmune Disease	$988	$1,083	$1,021
Lupus	$121	$134	$129
Myasthenia Gravis	$5	$5	$6
Psoriasis	$16	$17	$18
Scleroderma	$24	$24	$21
Food Allergies	$62	$73	$79
Vaccine Related	$2,236	$2,568	$2,139
Malaria Vaccine	$58	$64	$72
Vaccine Related (AIDS)	$598	$579	$574
Tuberculosis Vaccine	$61	$59	$99
Kidney and Urologic			
Kidney Disease	$649	$651	$661
Polycystic Kidney Disease	$31	$36	$39
Urologic Diseases	$546	$592	$604
Interstitial Cystitis	$11	$13	$17
Lung	$1,946	$2,458	$2,260
Acute Respiratory Distress Syndrome	$126	$158	$148
Chronic Obstructive Pulmonary Disease	$112	$121	$144
Cystic Fibrosis	$82	$94	$89

[2211] Name revised in FY 2018 from Septicemia.

Research Area (Dollars in Millions)*	FY 2019	FY 2020	FY 2021
Emphysema	$27	$49	$52
Neonatal Respiratory Distress[2212]	$79	$85	$72
Pneumonia	$146	$223	$153
Mental Health	$3,296	$3,577	$3,666
ADHD[2213]	$64	$72	$72
Depression	$578	$602	$610
Musculoskeletal			
Muscular Dystrophy	$83	$95	$82
Myotonic Dystrophy	$12	$24	$11
Duchenne/Becker Muscular Dystrophy	$34	$33	$27
Facioscapulohumeral Muscular Dystrophy	$10	$9	$9
Spinal Muscular Atrophy	$13	$8	$9
Osteogenesis Imperfecta	$12	$15	$13
Osteoporosis	$151	$148	$155
Paget's Disease	$2	$3	$3
Neurosciences	$9,468	$10,122	$10,716
Pain Research	$1,011	$846	$867
Fibromyalgia	$13	$24	$13
Headaches	$40	$42	$47
Migraines	$28	$28	$40
Chronic Pain[2214]	$856	$689	$725
Vulvodynia	$2	$2	$1
Reproductive System			
Adolescent Sexual Activity	$102	$88	$94
Teenage Pregnancy	$17	$11	$18
Contraception/Reproduction	$547	$593	$588
Endometriosis	$13	$14	$20
Fibroid Tumors (Uterine)	$17	$18	$16
Infertility	$151	$161	$192

[2212] Name revised in FY 2016 from "Perinatal - Neonatal Respiratory Distress Syndrome".
[2213] Name revised in FY 2021 from "Attention Deficit Disorder (ADD)".
[2214] Name revised in FY 2018 from "Pain Conditions – Chronic."

Appendix J: EUREKA Prize Competitions

NIH uses prize competitions, also known as challenges, to spark new ways of thinking, solve tough problems, stimulate innovation, and advance its core mission of turning discovery into health. Prize competitions enable NIH Institutes, Centers, and Offices (ICOs) to establish ambitious goals without bearing high levels of risk by paying only for results. This mechanism also affords NIH the opportunity to engage innovators across the country who have a wide range of skill sets and diverse backgrounds, but who typically may not be engaged in NIH research activities.

Section 2002 of the *21st Century Cures Act* (P.L. 114-255), enacted on December 13, 2016, requires NIH to support EUREKA prize competitions in areas of biomedical science that could realize significant advancements and/or improve health outcomes in human diseases and conditions that have a disproportionately small research investment relative to expenses for prevention and treatment, represent a serious and significant disease burden, or for which there is potential for significant return on investment. The *21st Century Cures Act* also requires NIH to report on the effect of innovations developed from EUREKA prize competitions on advancing biomedical science, improving health outcomes, and federal expenditures, and to include this information in the NIH triennial report. EUREKA prize competitions are carried out under authority granted to federal agencies by Section 24 of the *Stevenson-Wydler Technology Innovation Act of 1980* (1 U.S.C. 3719).

NIH, through NIA, began implementing the EUREKA prize authority in November 2017 through a request for public input on the feasibility of three potential prize competitions focused on AD and ADRD: validating predictors of AD progression, PET radiotracer to measure *in vivo* synaptic integrity, and low-cost innovation to improve systems of care for AD/ADRD patients and caregivers, and any other suggestions for AD/ADRD research goals to connect to a prize.[2215,2216] These efforts culminated in NIA's launching the first EUREKA prize competition on September 10, 2019 - The iCare-AD/ADRD. The iCare-AD/ADRD Challenge offered cash prizes totaling $400,000 to spur and reward the development of solutions for a technology-based application, fostering connections between relevant stakeholders to use technology, or the development of new technology applications to improve dementia care coordination and navigation. Effective dementia care management has been shown to improve outcomes, for example, by reducing behavioral and psychological symptoms of dementia and lowering health care costs by reducing emergency department visits, inpatient hospitalizations, and some readmissions.

Submissions for the iCare-AD/ADRD Challenge were accepted until June 30, 2019. The iCare-AD/ADRD Challenge enabled NIA to engage innovators across the country who had a wide range of skill sets and diverse backgrounds, including those who might not typically contribute to NIA research activities. A diverse collection of 33 individuals and teams (including established aging researchers, start-up companies and biotech firms) submitted applications to the Challenge. The technologies submitted

[2215] https://www.nih.gov/about-nih/who-we-are/nih-director/testimony-21st-century-cures-implementation-updates-fda-nih
[2216] https://grants.nih.gov/grants/guide/notice-files/NOT-AG-17-018.html

ranged from mobile apps to software platforms. In October 2019, NIA announced three winners in the iCare-AD/ADRD Challenge.[2217] The Atlanta-based MapHabit team, led by Stuart Zola, Ph.D., received the $250,000 first prize for their mobile device application that helps people with dementia follow simple commands to perform daily tasks, such as taking pills and brushing teeth, and also provides feedback to caregivers. This care management platform employs different interfaces depending on whether the user is a person with impaired memory, caregiver, or long-term care community manager. Caregivers can monitor adherence to medication schedules or track other activities. A second-place prize of $100,000 was awarded to a team from the University of California, Los Angeles, led by David Reuben, M.D. The web-based Dementia Care Software system, which was developed with High5LA in Los Angeles, helps specialists deliver care to many people with dementia. Because dementia requires both medical and social services, care management can be complex. The case management software, which integrates with the EHR system, has already been used at UCLA to coordinate the care of thousands of people. A final third place prize of $50,000 was awarded to a team led by Kristen Naney, Ph.D., at North Carolina Agricultural and Technical State University, Greensboro. The Caregiver 411 mobile device application enables dementia caregivers to foster social connections through a messaging center and obtain tailored resources related to mental, emotional, physical, social, legal, and financial concerns. The app also enables caregivers to find local health specialists and other professionals. By connecting caregivers and family members with targeted information, the Caregiver 411 app can help people make informed decisions at each stage of the dementia care journey.

Given the recency of these awards, more time is needed to better understand their impact. NIA will continue to monitor and measure the impact of the inaugural EUREKA prize competition and will report available information on its effects on research, health, and federal expenditures in the FY 2022–2024 report.

[2217] https://www.nia.nih.gov/news/winners-announced-national-institute-aging-dementia-care-coordination-challenge

Appendix K: Acronyms

Table 13: Acronyms

Acronym	Definition
2-ME	2-Methoxyestradiol
4C	COVID CDE Coordinating Committee
4DN	4D Nucleome
AAC	augmentative and alternative communication
AAMC	American Medical Colleges
AAV	Adeno-associated virus
AAV9	Associated Virus serotype 9
ABC-CT	Autism Biomarkers Consortium for Clinical Trials
ABCD	Adolescent Brain Cognitive Development℠
ACC	Autism Coordinating Committee
ACD	Advisory Committee to the Director
ACE	Autism Centers of Excellence
ACE2	Angiotensin-Converting Enzyme 2
ACL	Administration for Community Living
ACS	Acute coronary syndrome
ACT	Affordable Cancer Technologies
ACT NOW	Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome
ACTC	Alzheimer's Clinical Trials Consortium
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines initiative
ACTT	Adaptive COVID-19 Treatment Trial
AD	Alzheimer's Disease, or Atopic dermatitis
ADA	adenosine deaminase deficiency
ADA-SCID	adenosine deaminase deficiency-severe combined immunodeficiency
ADAPT-2	Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder
ADDM	Autism and Developmental Disabilities Monitoring Network
ADGC	Alzheimer's Disease Genetics Consortium
ADHD	attention-deficit hyperactivity disorder
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADORE	Alzheimer's And Dementia Outreach, Recruitment, And Engagement Resources
ADPKD	Autosomal dominant polycystic kidney disease
ADRC	Alzheimer's Disease Research Center
ADRD	Alzheimer's disease-related dementias
ADVANCE	Advancing Prevention Research for Health Equity

Acronym	Definition
AEIO	Autism Evaluation Implementation Oversight
AF	Annulus Fibrosus
AF4	Asymmetric-Flow Field-Flow
AFib	Atrial fibrillation
AFM	Acute Flaccid Myelitis
AGI	Audacious Goals Initiative
AHRQ	Agency for Healthcare Research and Quality
AI	artificial intelligence
AI/AN	American Indian and Alaska Native
AI/ML	artificial intelligence/machine learning
AIDS	Acquired immunodeficiency syndrome
AIM	Advancing Innovation through Mentorship
AIM-AHEAD	Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity
ALACRITY	Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness
alloHCT	allogenic hematopoietic cell transplant
alpha-syn	alpha-synuclein
ALS	amyotrophic lateral sclerosis
ALS2	Alsin Rho Guanine Nucleotide Exchange Factor
AMD	Age-related macular degeneration
AMI	Acute Myocardial Infarction
AML	acute myeloid leukemia
AMP	Accelerating Medicines Partnership®, or Antibody-Mediated Prevention
AMP-AD	Accelerating Medicines Partnership/Alzheimer's Disease
AMP-CMD	Accelerating Medicines Partnership® Common Metabolic Diseases
AMP-SCZ	Accelerating Medicines Partnership® Schizophrenia
ANA	Antinuclear antibody
AnVIL	Genomic Data Science Analysis, Visualization and Informatics Lab-space
AoA/ACL	Administration on Aging's Administration for Community Living
AoU	All of Us
APOLLO	APOL1 Long-term Kidney Transplantation Outcomes
APP	amyloid precursor protein, or Antiviral Program for Pandemics
AREDS	Age-Related Eye Disease Study
ARIC	Atherosclerosis Risk in Communities
ARISS	Amateur Radio on the International Space Station
ART	Antiretroviral Therapy
ASD	Autism Spectrum Disorders

Acronym	Definition
ASO	Antisense Oligonucleotides
ASPIRE	A Specialized Platform for Innovative Research Exploration
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention
ATR	Serine/threonine-protein
AUD	Alcohol use disorder
BABM	biological activity-based modeling
BARDA	Biomedical Advanced Research and Development Authority
BCERP	Breast Cancer and Environment Research Program
BCG	Bacille Calmette-Guerin
BCI	Brain-Computer Interface
BD2K	Big Data to Knowledge
BDI	Birth Defects Initiative
BE	Barrett's esophagus
BEST	Broadening Experiences in Scientific Training
BGTC	Bespoke Gene Therapy Consortium
BICCN	BRAIN Initiative Cell Census Network
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BMD	Becker muscular dystrophy
BMIC	BioMedical Informatics Coordinating Committee
bNAbs	broadly Neutralizing Antibodies
BP	Blood Pressure
BPN	Blueprint Neurotherapeutics Network
BRAIN	Brain Research Through Advancing Innovative Neurotechnologies® Initiative
BRCA	BReast CAncer gene
BRIM	Behavioral Research to Improve Medication-Based Treatment
BSE	Bovine Spongiform Encephalopathy
BSSR	Behavioral and Social Science Research
BUILD	Building Infrastructure Leading to Diversity
CA	cavernous angiomas
CAA	cerebral amyloid angiopathy
CAPN3	Calpain 3 gene
CAR	Chimeric antigen receptor
CARB	Combating Antibiotic Resistant Bacteria
CARD	Center for Alzheimer's and Related Dementias
CARES	*Coronavirus Aid, Relief, and Economic Security Act*
cART	Combination antiretroviral therapy
CAUSE	Childhood Asthma in Urban Settings
CBER	Center for Biologics Evaluation and Research

Acronym	Definition
CBT	Cognitive Behavioral Therapy
CC	NIH Clinical Center, or Collaborative Cross, or Coordinating Center
CCCs	Comorbidities, Co-infections, and Complications
CCDI	Childhood Cancer Data Initiative
CCRHB	Clinical Center Research Hospital Board
CCTN	Contraceptive Clinical Trials Network
CD2H	National Center for Data to Health
CDC	Centers for Disease Control and Prevention
CDCC	Coordination and Data Collection Center
CDE	Common Data Element
CEAL	Community Engagement Alliance
CEC	Coordination and Evaluation Center
CEERs	Centers of Excellence in ELSI Research
CEGS	Centers of Excellence in Genome Sciences
CEIRR	Centers of Excellence for Influenza Research and Response
CEIRS	Centers of Excellence for Influenza Research and Surveillance
CEPT	chroman 1, emricasan, polyamines, and trans-ISRIB
CF	Cystic fibrosis
CFDE	Common Fund Data Ecosystem
CFTR	Cystic fibrosis transmembrane conductance regulator
CGC	Cancer Grand Challenges
CGMHR	Center for Global Mental Health Research
CGR	Comparative Genomics Resource
CHIKV	Chikungunya Virus
ChiLDReN	Childhood Liver Disease Research Network
CHMI	Controlled Human Malaria Infection
CHMP7	Charged Multivesicular body Protein 7
CIFASD	Collaborative Initiative on Fetal Alcohol Spectrum Disorders
CISNET	Cancer Intervention and Surveillance Network
CIT	Center for Information Technology
CIVICS	Collaborative Influenza Vaccine Innovation Centers
CJD	Creutzfeldt-Jakob Disease
CKD	Chronic kidney disease
cLBP	Chronic low back pain
CLIA	Clinical Laboratory Improvement Amendments
ClinGen	Clinical Genome
CMD	Congenital muscular dystrophies
CMPHIR	Center for Microbial Pathogenesis and Host Inflammatory Responses

Acronym	Definition
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
CoARS	Consortium on Addiction Recovery Science
COBRE	Centers of Biomedical Research Excellence
COE	Centers of Excellence
CollegeAIM	College Alcohol Intervention Matrix
ComPASS	Community Partnerships to Advance Science for Society
COMPILE	Continuous Monitoring of Pooled International Trials of ConvaLEscent Plasma for COVID-19 Hospitalized Patients
CONNECTS	Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies
COPD	Chronic obstructive pulmonary disease
COPE	COVID-19 Participant Experience
COSWD	Chief Officer for Scientific Workforce Diversity
COVID-19	Coronavirus Disease 2019
CP	cerebral palsy
CP-CTNet	Cancer Prevention Clinical Trials Network
CPAG	Coalition for Patient Advocacy Groups
CPDPC	Chronic Pancreatitis Diabetes Pancreas Cancer
CPSTF	Community Preventive Services Task Force
CPTAC	Clinical Proteomic Tumor Analysis Consortium
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
CRC	Colorectal Cancer
CRDC	Cancer Research Data Commons
CREID	Centers for Research in Emerging Infectious Diseases
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRN	Coordinated Registry Network
CROMS	Clinical Research Operations and Management System
cryo-EM	cryo-electron microscopy
cryoET	cryo-electron tomography
CSBR-AOC	Contributions of Social and Behavioral Research in Addressing the Opioid Crisis
CSCPDPC-CDMC	Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer: Coordinating and Data Management Center
CSER	Clinical Sequencing Evidence-Generating Research
CSF	Cerebrospinal fluid
CSR	Center for Scientific Review
CT	Computed tomography
CTAC	Clinical Trials And Translational Research Advisory Committee
CTE	Chronic Traumatic Encephalopathy

Acronym	Definition
CTN	Clinical Trials Network
CTP	FDA Center for Tobacco Products
CTR	Clinical and Translational Research
CTSA	Clinical and Translational Science Awards
CTSN	Cardiothoracic Surgical Trials Network
CVD	Cardiovascular disease
CWD	Chronic Wasting Disease
DAP	Diversity Action Plan
DATA	Data and Technology Advancement
DBS	Deep brain stimulation
DCC	Data Coordinating Center
DCCT	Diabetes Control and Complications Trial
DEBUT	Design by Biomedical Undergraduate Teams
DEIA	Diversity, Equity, Inclusion, and Accessibility
DENV	Dengue Virus
DES	Diethylstilbestrol
DFC	Diabetic Foot Consortium
dGTEx	developmental Genotype-Tissue Expression
DHH	Deaf or hard of hearing
DIDRT	Duke Infectious Disease Response Training
DILI	Drug-induced liver injury
DLL3	Delta-Like 3
DMCC	Data Management and Coordinating Center
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic Acid
DNDi	Drugs for Neglected Diseases initiative
DNTP	Division of the National Toxicology Program
DOE	Department Of Energy
DPC	Diversity Program Consortium
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DR2	Disaster Research Response
DRC	Democratic Republic of the Congo
DREAM	Drug Repurposing for Effective Alzheimer's Medicines
DS	Down Syndrome
DSID	Dietary Supplement Ingredient Database
DSLD	Dietary Supplement Label Database
DSP	Distinguished Scholars Program
DSRCC	NIH Dietary Supplement Research Coordination Committee

Acronym	Definition
DUX4	Double homeobox, 4
EBOV	Ebola Virus gene insert
EBV	Epstein-Barr virus
ECHO	Environmental influences on Child Health Outcomes
EDI	Office of Equity, Diversity, and Inclusion
EDIC	Epidemiology of Diabetes Interventions and Complications study
EDRN	Early Detection Research Network
EEEV	Equine Encephalitis Virus
EEG	Electroencephalogram
EHE	Ending the HIV Epidemic
EHR	Electronic health record
EHS	Environment, Health, and Science
ELF1	E74-Like ETS transcription Factor 1
ELSI	ethical, legal and social implications
EMA	European Medicines Agency
eMERGE	Electronic Medical Records and Genomics
EMR	electronic medical record
EMS	Emergency Medical Services
EMT-TF	Epithelial-Mesenchymal Transition-Transcription Factors
ENCODE	Encyclopedia Of DNA Elements
EPINET	Early Psychosis Intervention Network
EPPIC-Net	Early Phase Pain Investigation Clinical Network
ER	estrogen receptor
ESI	Early-Stage Investigator
ESI/ECI	Early-Stage Investigator/Early career investigator
ESRD	End-Stage Renal Disease
ESSP	Early-Stage Surgeon Scientist Program
ESTEEMED	Enhancing Science, Technology, EnginEering, and Math Educational Diversity
EUA	emergency use authorization
EUREKA	Exceptional, Unconventional Research Enabling Knowledge Acceleration
EV	Extracellular vesicle
EVALI	e-cigarette or vaping use-associated lung injury
EVD	Ebola Virus Disease
EXPLORER	Extreme Performance Long axial Research scanneR
exRNA	Extracellular RNA
FAIR	findable, accessible, interoperable, and reusable
FAR	Federal Acquisition Regulation
FASDs	Fetal alcohol spectrum disorders

Acronym	Definition
FCR	Fostering Cohort Recruitment
FDA	Food and Drug Administration
FDA CTP	FDA Center for Tobacco Products
FHIR	Fast Healthcare Interoperability Resource
FIC	Fogarty International Center
FIRST	Faculty Institutional Recruitment For Sustainable Transformation
fMRI	functional magnetic resonance imaging
FNIH	Foundation for the National Institutes of Health
FOA	Funding Opportunity Announcement
FRLC	Future Research Leaders Conference
FSHD	Facioscapulohumeral muscular dystrophy
FWGoDS	Federal Working Group on Dietary Supplements
FXS	Fragile X Syndrome
FY	Fiscal Year
GAD	Generalized anxiety disorder
GAO	Government Accountability Office
GFAP	glial fibrillary acidic protein
GI	Gastrointestinal
GO MOMs	Glycemic Observation and Metabolic Outcomes in Mothers and Offspring study
GPA	Granulomatosis with polyangiitis
GPRA	Government Performance and Results Act
GRADE	Glycemia Reduction Approaches in Diabetes: An Effectiveness Study
GRAVID	Gestational Research Assessments for COVID-19
GREGoR	Genomics Research Elucidates Genetics of Rare Disease
GREI	Generalist Repository Ecosystem Initiative
GRK2	G protein-coupled receptor kinase 2
GSP	Genome Sequencing Program
GTEx	Genotype-Tissue Expression
GTP	Genome Technology Program
GWAS	genome-wide association studies
H3Africa	Human Heredity and Health in Africa
HA	Hemagglutinin
HaAD	Health and Aging Data [Enclave]
HaH	Hospital at Home care
HAT	Human African Trypanosomiasis
HBCD	HEALthy Brain and Child Development
HBV-ALF	Hepatitis B Virus-associated Acute Liver Failure
HCC	hepatocellular carcinoma

Acronym	Definition
HEAL	Helping to End Addiction Long-term® Initiative
HELIX	Human Early-Life Exposome
HER	electronic health records
HER2	human epidermal growth factor receptor 2
HES	Hypereosinophilic syndromes
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HGPS	Hutchinson-Gilford progeria syndrome
HGSOC	High-grade serous ovarian cancer
HGVS	Human Genome Variation Society
HHEAR	Human Health Exposure Analysis Resource
HHS	Health and Human Services
HIF-2a	Hypoxia-inducible factor-2a
HIPAA	Health Insurance Portability And Accountability Act
hiPSCs	Human induced pluripotent stem cells
HIRN	Human Islet Research Network
HIV	human immunodeficiency virus
HOPE	Hemodialysis Opioid Prescription Effort
HPV	human papilloma virus
HRCT	High-resolution computed tomography
HRS	Health and Retirement Study
HRT	hormone replacement therapy
HS	Hidradenitis suppurativa
HSCs	Hematopoietic stem cell
HuBMAP	Human BioMolecular Atlas Program
IACC	Interagency Autism Coordinating Committee
IAL	Inclusion Across the Lifespan
IAP	Intestinal Alkaline Phosphatase
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IC	Institutes and Centers
iCD	ileal Crohn's disease
ICEMR	International Centers of Excellence for Malaria Research
ICER	International Centers for Excellence In Research
ICI	Immune checkpoint inhibitors
ICOs	Institutes, Centers, and Offices
IDD	intellectual and developmental disabilities
IDDRC	Intellectual and Developmental Disabilities Research Centers

Acronym	Definition
IDeA	Institutional Development Award
IDeaS	Impact of Rare Diseases on Patients and Healthcare Systems
IeDEA	International epidemiology Databases to Evaluate AIDS
IFN	interferon
Ig	immunoglobulin
IGF-1	Insulin-like growth factor 1
IGNITE	Implementing Genomic in Practice
IHS	Indian Health Service
IIPC	International Internet Preservation Consortium
IL	interleukin
ILC	Innate Lymphoid Cells
ILD	Interstitial lung disease
IMPACC	Immunophenotyping Assessment In A COVID-19 Cohort
IMPACT	Imbedded Pragmatic Alzheimer's disease and AD-Related Dementias Clinical Trials
IMPOWR	Integrative Management of Chronic Pain and OUD for Whole Recovery
INBRE	IDeA-State Networks of Biomedical Research Excellence
INCLUDE	INvestigation of Co-occurring conditions across the Lifespan to Understand Down Syndrome
IND	Investigational New Drug
iPSCs	induced Pluripotent Stem Cells
IRACDA	Institutional Research And Academic Career Development Awards
IRB	Institutional Review Board
IRP	Intramural Research Program
ISCC-PEG	Inter-Society Coordinating Committee for Practitioner Education In Genomics
ISPCTN	IDeA States Pediatric Clinical Trials Network
IT	information technology
ITAP	Independent Test Assessment Program
ITP	Interventions Testing Program
ITRB	Information Resources Technology Branch
IU	Indiana University
IUD	Intrauterine devices
IVIS	in vivo imaging systems
JCOIN	Justice Community Opioid Innovation Network
JDM	Juvenile dermatomyositis
KLK6	Kallikrein-related peptidase 6
KOMP2	Knockout Mouse Phenotyping Program
KS	Kaposi Sarcoma
LATE	Limbic-predominant Age-related TDP-43 Encephalopathy

Acronym	Definition
LDL	Low-density lipoprotein
LDRC	Learning Disabilities Research Centers
LEAF	Life Enhancing Activities for Family Caregivers
LET	Linear Energy Transfer
LGMD	Limb-girdle muscular dystrophies
LGMDR1	Limb girdle muscular dystrophy recessive type 1
LGMDR9	Limb girdle muscular dystrophy recessive type R9
LGSOC	low-grade serous ovarian cancer
LINCS	Library of Integrated Network-based Cellular Signatures
LMICS	low- and middle-income countries
LNPs	Lipid nanoparticles
LRP	NIH Loan Repayment Programs
LRP-HDR	Loan Repayment Program for Health Disparities Research
LRP-REACH	Loan Repayment Program for Research in Emerging Areas Critical to Human Health
LS	Lynch syndrome
LSCC	Lung Squamous Cell Carcinoma
LURN	Lower Urinary Tract Dysfunction Research Network
LUTS	Lower urinary tract symptoms
mAb	monoclonal Antibody
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MATCH	Molecular Analysis for Therapy Choice
MAVS	mitochondrial antiviral signaling
MC3R	Melanocortin-3 receptor
MCADD	Medium chain acyl-coA dehydrogenase deficiency
McpC	Methyl-accepting chemotaxis protein C
MCT1	Monocarboxylate transporter 1
MDSRC	Muscular Dystrophy Specialized Research Centers
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
MERS	Middle East Respiratory Syndrome
MeSH	Medical Subject Headings
MFMU	Maternal-Fetal Medicine Units
mHealth	mobile health
MIDAS	Models of Infectious Disease Agents Study
MIDRC	Medical Imaging and Data Resource Center
MIND	Memory and Cognition in Decreased Hypertension
MIRA	Maximizing Investigators' Research Award
MIS-C	Multisystem Inflammatory Syndrome in Children
ML	Machine Learning

Acronym	Definition
MMM	Maternal Morbidity and Mortality
MMWR	Morbidity and Mortality Weekly Report
MONEAD	Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs
MorPhiC	Molecular Phenotypes of Null Alleles in Cells
MOSAIC	Maximizing Opportunities for Scientific and Academic Independent Careers Program
MoTrPAC	Molecular Transducers of Physical Activity Consortium
MRI	magnetic resonance imaging
mRNA	Messenger Ribonucleic Acid
MRS	Magnetic Resonance Spectroscopy
MS	Multiple sclerosis
MSCs	Mesenchymal stem cells
Mtb	*Mycobacterium tuberculosis*
MTI	Medical Text Indexer
MTX	Methotrexate
N3C	National COVID Cohort Collaborative
NA	Neuraminidase
NAC	N-acetylcysteine
NACA	National Advisory Council on Aging
NACC	National Alzheimer's Coordinating Center
NAEC	NIH AIDS Executive Committee
NAFLD	Nonalcoholic fatty liver disease
NAMHC	National Advisory Mental Health Council
NAPA	National Alzheimer's Project Act
NARI	Native American Research Internship
NARMS	National Antibiotic Resistance Monitoring System
NAS	Neonatal Abstinence Syndrome
NASEM	National Academies of Science, Engineering, and Medicine
NCANDA	National Consortium on Alcohol and Neurodevelopment in Adolescence
NCATS	National Center for Advancing Translational Sciences
NCBI	National Center for Biotechnology Information
NCCAPS	NCI COVID-19 in Cancer Patients Study
NCCIH	National Center for Complementary and Integrative Health
NCDS	National Center for Data Services
NCI	National Cancer Institute
NCMHD	National Center on Minority Health and Health Disparities
NCMRR	National Center for Medical Rehabilitation Research
NCORP	NCI Community Oncology Research Program
NCPI	NIH Cloud Platform Interoperability

Acronym	Definition
NCRAD	National Centralized Repository for AD/ADRD
NCTRI	National Centers for Translational Research in Reproduction and Infertility
NDA	NIMH Data Archive
NDAFW	National Drug and Alcohol Facts Week
NDAR	National Database for Autism Research
NDEWS	National Drug Early Warning System
NDI	National Death Index
NE	Neuroendocrine
NEC	NIH Equity Committee
NEC	Necrotizing enterocolitis
NEHEP	NEI's National Eye Health Education Program
NEI	National Eye Institute
NEI AGI	NIE Audacious Goals Initiative
NEO	NIH Ethics Office
NeuroCOVID	COVID-19 Neuro Databank/Biobank
NF1	neurofibromatosis type 1
NfL	neurofilament light
NGRI	Next Generation Researchers' Initiative
NGS	next-generation DNA-sequencing
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NHP	nonhuman primate
NHP dGTEx	Non-Human Primate Developmental Genotype-Tissue Expression project
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, Musculoskeletal, and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
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
NIEHS RISE	NIEHS Research Intensive Short Courses and Educational Opportunities
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health

Acronym	Definition
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
NLM	National Library of Medicine
NMNH	National Museum of Natural History
NNLM	Network of the National Library of Medicine
NOSI	Notice of Special Interest
NOWS	Neonatal/Newborn opioid withdrawal syndrome
NP	Nucleus Pulposus
NPC	NCATS Pharmaceutical Collection
NPH	Nutrition for Precision Health powered by the *All of Us* Research Program
NPRCs	National Primate Research Centers
NRMN	National Research Mentoring Network
NRN	Neonatal Research Network
NRSA	Ruth L. Kirschstein National Research Service Award
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NSDUH	National Survey on Drug Use and Health
NSF	National Science Foundation
NSRRC	National Swine Resource and Research Center
NTP	National Toxicology Program
OA	Osteoarthritis
OAIC	Older Americans Independence Centers
OALM	Office Of Acquisitions Logistics And Management
OAR	Office of AIDS Research
OARAC	NIH Office of AIDS Research Advisory Council
OBSSR	Office of Behavioral and Social Sciences Research
OCIO	Office of the Chief Information Officer
OCPL	Office of Communications and Public Liaison
OCT	Optical coherence tomography
OD	Office of the Director
ODEO	OD Executive Office
ODP	Office of Disease Prevention
ODS	Office of Dietary Supplements
ODSS	Office of Data Science Strategy
ODWD	Office for Disparities Research and Workforce Diversity
OER	Office of Extramural Research

Acronym	Definition
OFACP	Office of Federal Advisory Committee Policy
OFC	Orofacial cleft
OGC	The NIH Branch of the HHS Office of the General Counsel's (OGC) Public Health Division
OIR	Office of Intramural Research
OITE	Office Of Intramural Training and Education
OLPA	Office of Legislative Policy and Analysis
OM	Office of Management
OMRI	Overhauser Enhanced Magnetic Resonance Imaging
ONR	Office of Nutrition Research
OOCCR	Office of Ombudsman/Center for Cooperative Resolution
ORIP	Office of Research Infrastructure Programs
ORWH	Office of Research on Women's Health
OSC	Office of Strategic Coordination
OSP	Office of Science Policy
OTA	Other Transactions Authority
OUD	Opioid Use Disorder
P.L.	Public Law
P2P	Pathways to Prevention
PACs	polycyclic aromatic compounds
PAGs	patient advocacy groups
PASC	Post-Acute Sequalae of SARS-CoV-2 infection
PATH	Population Assessment of Tobacco and Health
PaVe-GT	Platform Vector Gene Therapy
PBB 153	Polybrominated biphenyl 153
PBRN	Practice-Based Research Network
PCDH1	Protocadherin-1
PCOS	Polycystic ovary syndrome
PD	Parkinson's disease, or Pathogen Detection
PDAC	Pancreatic ductal adenocarcinoma
PEM	Post-exertional malaise
PEP	Post-Exposure Prophylaxis
PET	Positron Emission Tomography
PF	Pulmonary fibrosis
PFAS	Per- and polyfluoroalkyl substances
PFS	Pittsburgh Fatigability Scale
PGC	Psychiatric Genomics Consortium
PHACS	Pediatric HIV/AIDS Cohort Study

Acronym	Definition
PHN	Pediatric Heart Network
PHR	patient health record
PHS	Public Health Service
PICU	Pediatric Intensive Care Unit
PIDDs	Primary immune deficiency diseases
PII	Personally Identifiable Information
PLUS	Prevention of Lower Urinary track Symptoms
PM	Particulate matter
PM2.5	fine particulate matter air pollution
PMACC	Precision Medicine Analysis and Coordination Center
PMC	PubMed Central, or Pain Management Collaboratory
PMC-OA	PubMed Central Open Access
POAG	Primary open angle glaucoma
PPACT	Collaborative Care for Chronic Pain in Primary Care
PPC	Preferred Product Characteristics
PR	Pulmonary rehabilitation
PRAMM	Pregnancy-Related or Associated Morbidity and Mortality
PRAMS	Pregnancy Risk Assessment Monitoring System
PRECISIONS	Prospective tReatment EffiCacy in IPF uSIng genOtype for Nac Selection
PrEP	Pre-Exposure Prophylaxis
PRES	Prevention Research Expertise Survey
PREVENT	Preclinical Drug Development Program
PRIME	Preinflammatory Mesenchymal
PRIMED	Polygenic Risk MEthods in Diverse populations
PRISM	Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid
PRO-TECT	PRedictiOn Algorithms for The DeTECTion Of Early Stage Pancreatic Cancer
PROMIS®	Patient-Reported Outcomes Measurement Information System®
PsA	Psoriatic arthritis
PSI-BLAST	Position-Specific Iterating BLAST
PSPP	Preclinical Screening Platform for Pain
PSRC	Prevention Sciences Review Committee
PTEN	Phosphatase and tensin homolog
PTHR1	Parathyroid Hormone Receptor Type-1
PTLDS	Post-treatment Lyme Disease Syndrome
PVI	Pandemic Vulnerability Index
RA	Rheumatoid arthritis
radCDCC	RADx-rad Consortium Data and Coordination Center
RADIANT	Rare and Atypical Diabetes Network

Acronym	Definition
RADx	Rapid Acceleration of Diagnostics
RADx-ATP	Rapid Acceleration of Diagnostics Advanced Technology Platforms
RADx-rad	Rapid Acceleration of Diagnostics Radical
RADx-UP	Rapid Acceleration of Diagnostics Underserved Populations
RAS	Researcher Auth Service
RCCN	Research Centers Collaborative Network
RCDC	Research, Condition, and Disease Classification
RCMAR	Resource Centers for Minority Aging Research
RCRA	Recalcitrant Cancer Research Act
RDCRC	Rare Diseases Clinical Research Consortia
RDCRN	Rare Diseases Clinical Research Network
RDCRN-DW	RDCRN Data Warehouse
RDoC	Research Domain Criteria Initiative
RDS	Respiratory distress syndrome
REACH	Research Evaluation and Commercialization Hubs, or Resiliency, Environmental Action, and Collaborations for Health
RECOVER	Researching COVID to Enhance Recovery
REDS	Recipient Epidemiology and Donor Evaluation Study
REEP	Racial and Ethnic Equity Plan
REI	Racial Equity Initiative
RESTV	Reston Ebolavirus
RFI	Request For Information
RGCs	Retinal ganglion cells
RIE	Relative Immunological Effectiveness
RISE	Restoring Insulin Secretion
RMS	rhabdomyosarcoma
RNA	ribonucleic acid
ROP	Retinopathy of prematurity
RPG	Research Project Grant
RS1	Retinoschisin
RSV	Respiratory Syncytial Virus
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SA	*Staphylococcus aureus*
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SASP	Senescence-Associated Secretory Phenotype
SBE COVID	Social, Behavioral, and Economic Health Impacts of COVID-19
SBIR	Small Business Innovation Research

Acronym	Definition
SBP	Systolic Blood Pressure
SCAN	Standardized Centralized Alzheimer's and Related Dementias Neuroimaging
SCD	Sickle cell disease
SCGB	Secretoglobin
SCGE	Somatic Cell Genome Editing
SCID	Severe combined immunodeficiency
SCLC	Small Cell Lung Cancer
scMEP	single-cell metabolic regulome profiling
SCORE	Support for Competitive Research
SCTL	Stem Cell Translation Laboratory
SDoH	social determinants of health
SEARCH	SEARCH for Diabetes in Youth Study
SEED	Office of Small business Education and Entrepreneurial Development
SEER	Surveillance, Epidemiology, and End Results
SenNet	Cellular Senescence Network
SEPA	Science Education Partnership Award
SeroNet	Serological Sciences Network
SERRT	Spacer Enabled Robust Radiation Therapy
SES	socioeconomic status
SGM	Sexual and Gender Minority
SGMRO	Sexual and Gender Minority Research Office
ShA9	*Staphylococcus hominis A9*
SHAG	Spatiotemporal Health Analytics Group
SHINE	Stimulating Hematology Investigation: New Endeavors
SIDS	Sudden infant death syndrome
SIGs	scientific interest groups
SIREN	Strategies to Innovate EmeRgENcy Care Clinical Trials Network
SLE	Systemic lupus erythematosus
SMA	Spinal Muscular Atrophy
SMM	Severe maternal morbidity
SNA	Social network analysis
SOBC	Science of Behavior Change [program]
SOS	Subcommittee on Open Science
SOX2	SRY-Box Transcription Factor 2
SPAD	Sponsored Programs Administration Development
SPAN	Stroke Preclinical Assessment Network, or Study of Pregnancy And Neonatal Health
SPARC	Stimulating Peripheral Activity to Relieve Conditions

Acronym	Definition
SPHERES	SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance
SPRINT	Systolic Blood Pressure Intervention Trial
SPRINT-MIND	Systolic Blood Pressure Intervention Trial Memory and Cognition In Decreased Hypertension
SRA	Sequence Read Archive
SRG	Scientific Review Group
SSc	Systemic sclerosis
SSc-ILD	Systemic scleroderma associated interstitial lung disease
STAR	Supplements To Advance Research
STEM	Science, Technology, Engineering, and Mathematics
STIs	sexually transmitted infections
STOP	Subthreshold Opioid Use Disorder Prevention
STRIDES	Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability
STTR	Small Business Technology Transfer
SUD	Substance use disorder
SWD	Office of the Chief Officer for Scientific Workforce Diversity
SWDSS	Scientific Workforce Diversity Seminar Series
SYCT	Say Yes! COVID Test
synNOTCH	synthetic Notch
T2D	type 2 diabetes
T2T	Telomere-to-Telomere
TABA	Technical And Business Assistance
TARGET	Therapeutically Applicable Research to Generate Effective Treatments
TB	Tuberculosis
TBD	tickborne diseases
TBI	Traumatic Brain Injury
TCGA	The Cancer Genome Atlas
TCORS	Tobacco Centers of Regulatory Science
TDM	Technology and digital media
TEDDY	The Environmental Determinants of Diabetes in the Young
Tfh13	T follicular helper cell 13 (Tfh13 cells)
TGD	Transgender/Gender-Diverse
THC	Tetrahydrocannabinol
THRO	Tribal Health Research Office
TKA	total knee arthroplasty
TKR	Total knee replacement
tMDS/AML	therapy-related myelodysplastic syndrome/acute myeloid leukemia

Acronym	Definition
TME	Tumor Microenvironment
TNF	tumor necrosis factor
TOF	Tetralogy of Fallot
TOLLIP	Toll Interacting Protein
TOP1	Topoisomerase 1
TOPMed	Trans-Omics for Precision Medicine
TPP	Target Product Profile
TRACE	Tracking Resistance and Coronavirus Evolution
TRAP	Traffic-related air pollution
TREAT-AD	Target Enablement to Accelerate Therapy Development for Alzheimer's Disease
TRND	Therapeutics for Rare and Neglected Diseases
TRPA1	Transient receptor potential ankyrin 1
TRSP	Tobacco Regulatory Science Program
TSA-Seq	tyramide signal amplification sequencing
TSC	tuberous sclerosis complex
TSE	Tobacco smoke exposure, or Transmissible Spongiform Encephalopathies
TSIF	Translational Science Interagency Fellowship
U.K.	United Kingdom
U.S.	United States
UAMS	University of Arkansas for Medical Sciences
UDN	Undiagnosed Diseases Network
UHCA	Ultra-High Content Analysis
UI	Urinary incontinence
UPEC	*Uropathogenic Escherichia coli*
USDRN	Urinary Stone Disease Research Network
USDS	United States Digital Service
USPS	United States Postal Service
USPSTF	U.S. Preventive Services Task Force
UTI	Urinary tract infections
UV	Ultraviolet
VA	U.S. Department of Veterans Affairs
VADR	Viral Annotation DefineR
VCID	vascular cognitive impairment/dementia
VEXAS	vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome
VHL	von Hippel-Lindau
VSV	Vesicular Stomatitis Virus
WGD	Working Group on Diversity
WGDBRW	Working Group on Diversity in the Biomedical Research Workforce

Acronym	Definition
WHO	World Health Organization
WNV	West Nile virus
WTP	Worker Training Program
XLRS	X-linked retinoschisis
ZIKV	Zika virus
ZIP	Zika In Infants and Pregnancy
ZIRC	Zebrafish International Resource Center
ZMAT3	Zinc Finger Matrin-Type 3